



Multidisciplinary Approaches to Cancer Symposium

Debate: ctDNA Should Be Incorporated Into Active Management of Colorectal Cancer Patients ~ Focus: Pro argument

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City of Hope

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Disclosures

- Consultant for Agenus, Astellas, AstraZeneca, Bayer, BostonGene, Daiichi Sankyo, Eli Lilly, Elicio Therapeutics, Foundation Medicine, Guardant Health, Illumunia, Merck, Natera, Neogenomics, Regeneron, SAGA Diagnostics, SeaGen, Taiho, Tempus, Xilio
- Founder of Precision BioSciences
- Grant/Research for Agenus, Merck, Novartis; and Scientific Board Advisor for Elicio Therapeutics

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.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Utility of ctDNA testing/liquid biopsies across cultures, and in terms of young onset colorectal cancer, assessing/weighing its impact across patients from all backgrounds. Highlighting commonalities and differences among individuals in this patient population. And challenges and needs that would be appropriate to address*
- *Highlighting disparities and access when it comes to young onset colorectal cancer.*

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

SECTIONS

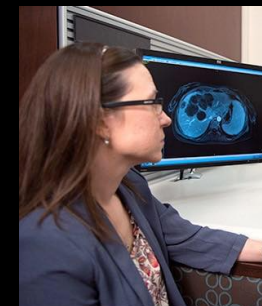
HOME

SEARCH

The New York Times

WELL | LIVE

More Young People Are Dying of Colon Cancer



The New York Times

Well

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Colon and Rectal Cancers Rising in Young People

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What Young People Need to Know About Colon Cancer

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t

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167

BLACK & YOUNG ADULTS AT
HIGHER RISK
OF COLON
CANCER

Chadwick Boseman's
diagnosis at a young age
was not unusual among
colon cancer patients

Franciscan HEALTH



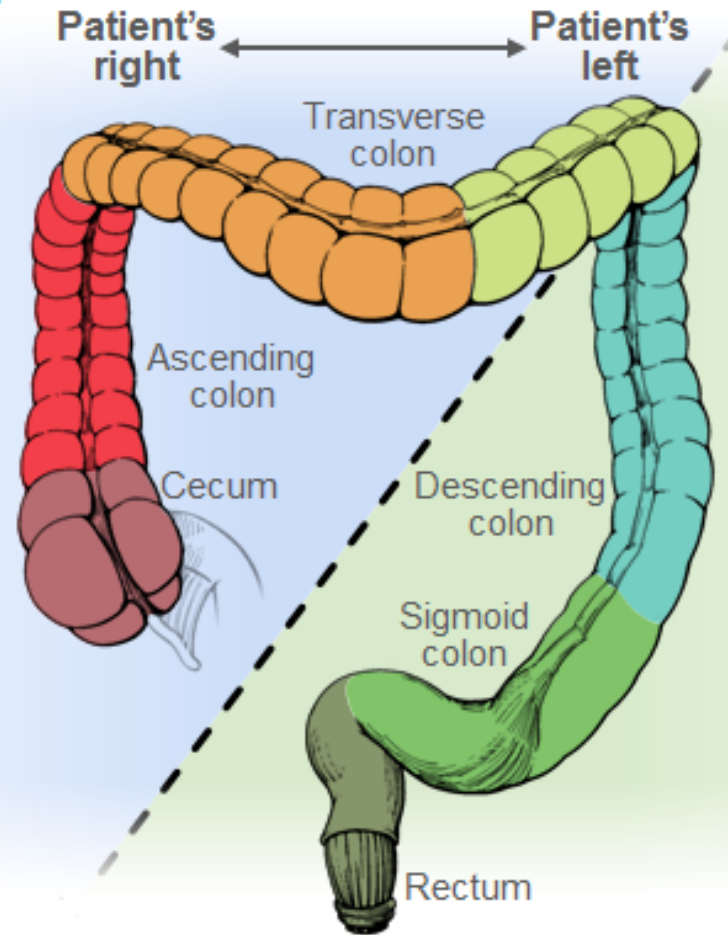
RIGHT vs. LEFT

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}

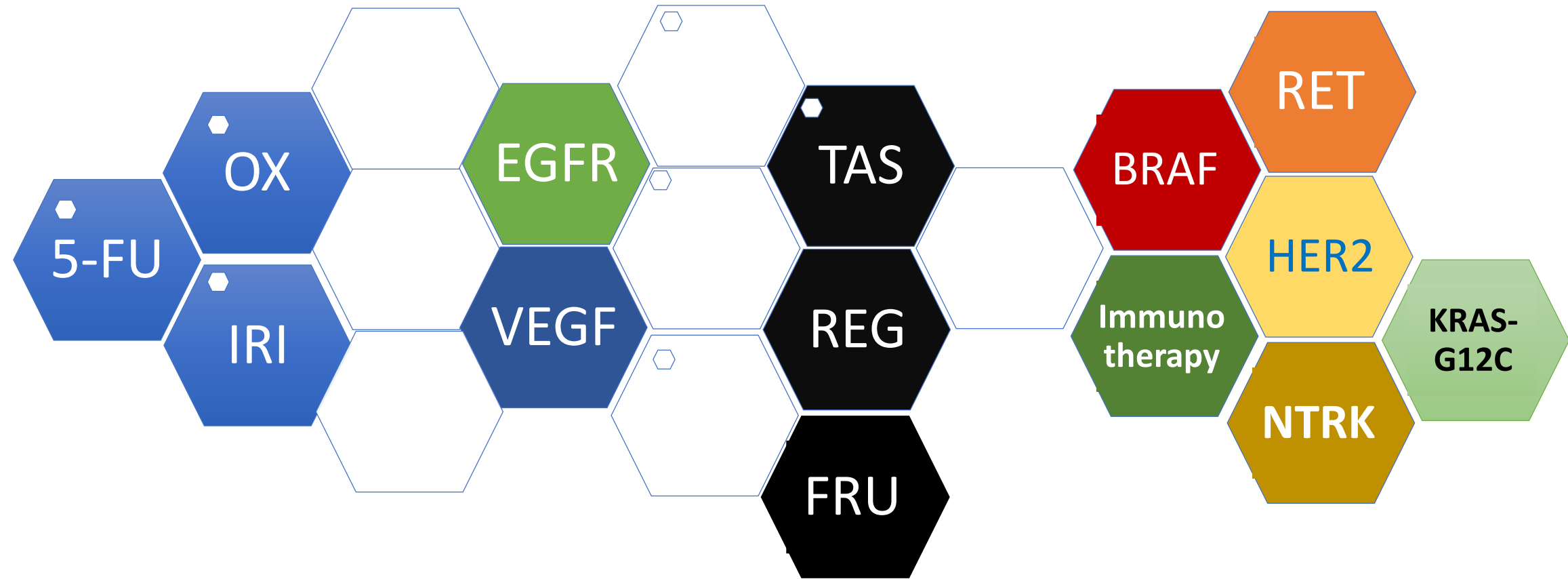


MEK

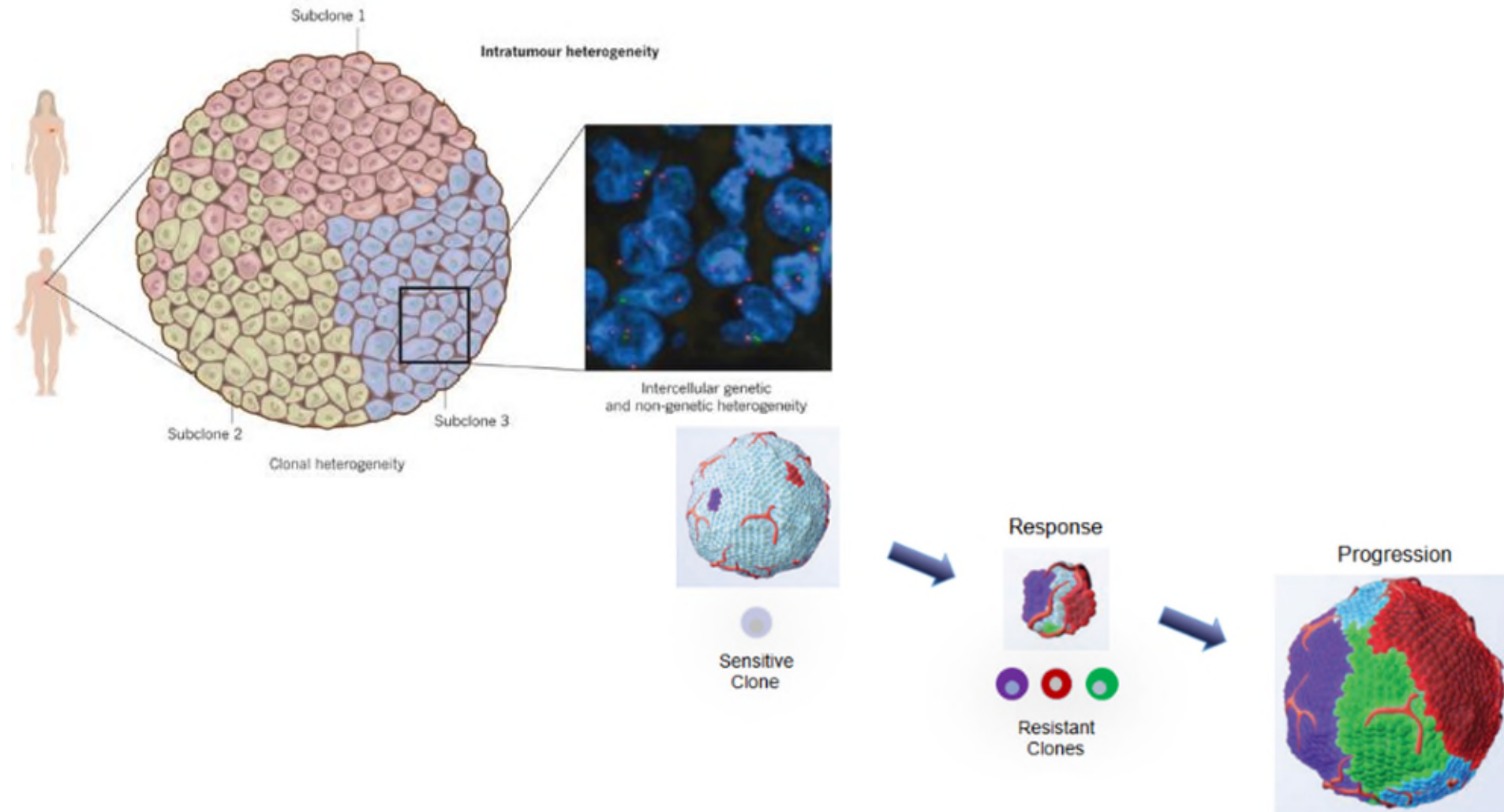


ERK

Treatment options for patients with mCRC



Intratumoral and temporal heterogeneity





ctDNA: Dawn of a New Era

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

SPECIAL SERIES: PRECISION MEDICINE AND IMMUNOTHERAPY IN GI MALIGNANCIES

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

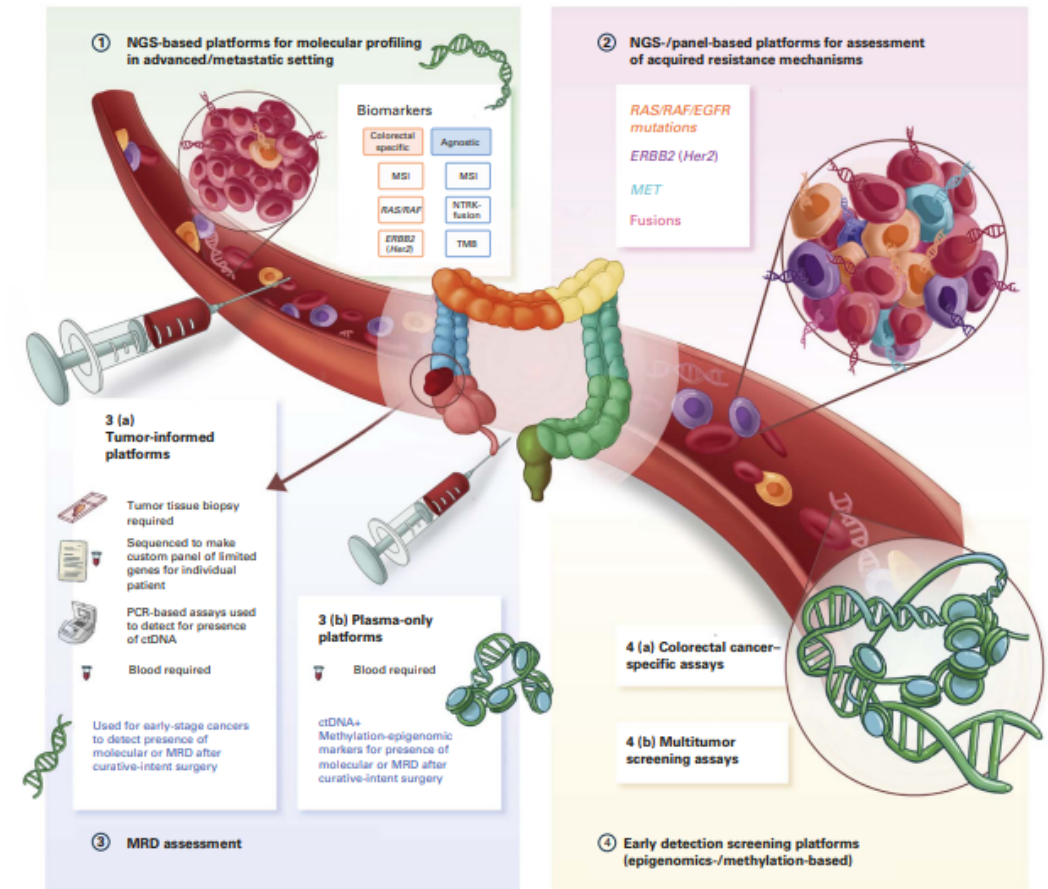
Midhun Malla, MD, MS¹; Jonathan M. Loree, MD, MS²; Pashtoon Murtaza Kasi, MD, MS³; and Aparna Raj Parikh, MD⁴

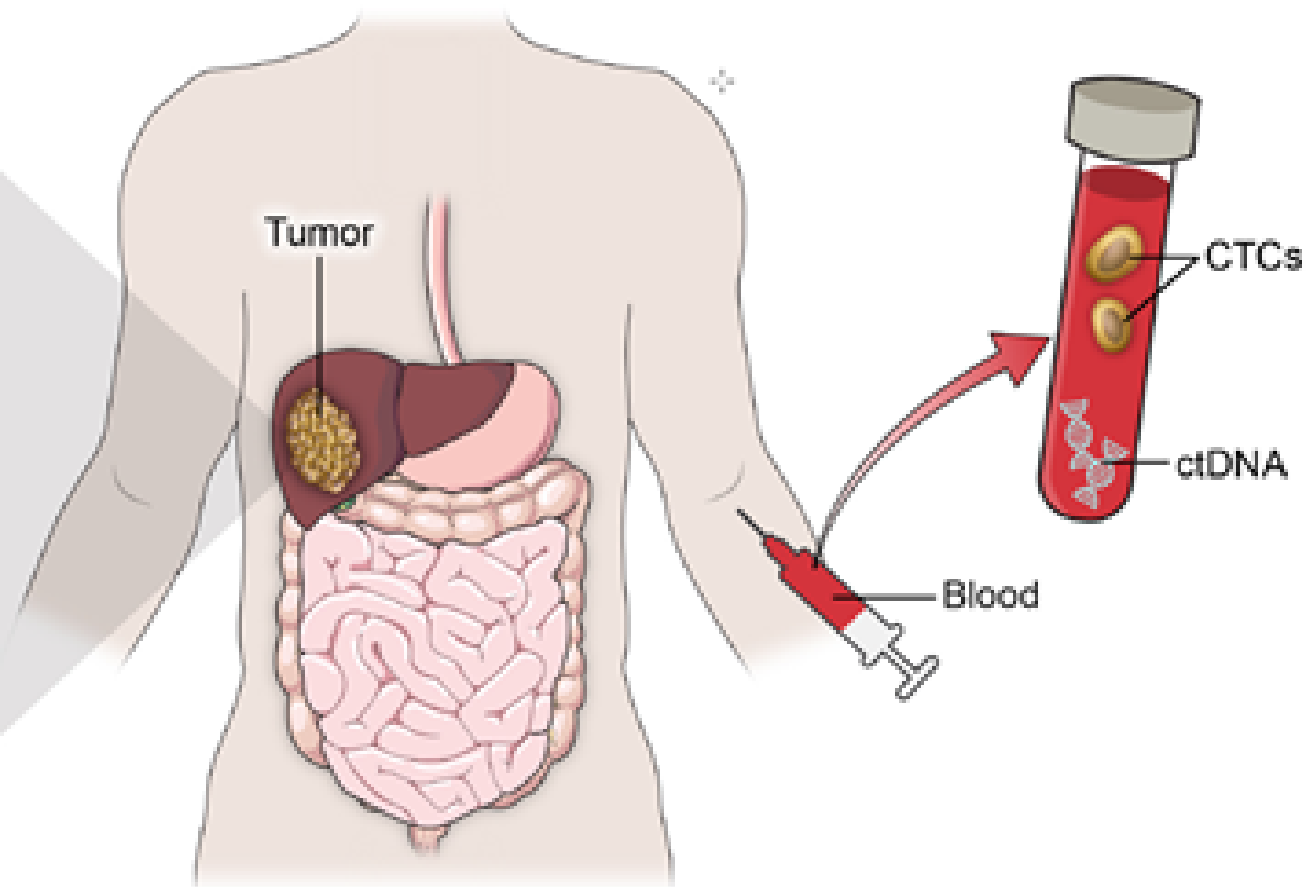
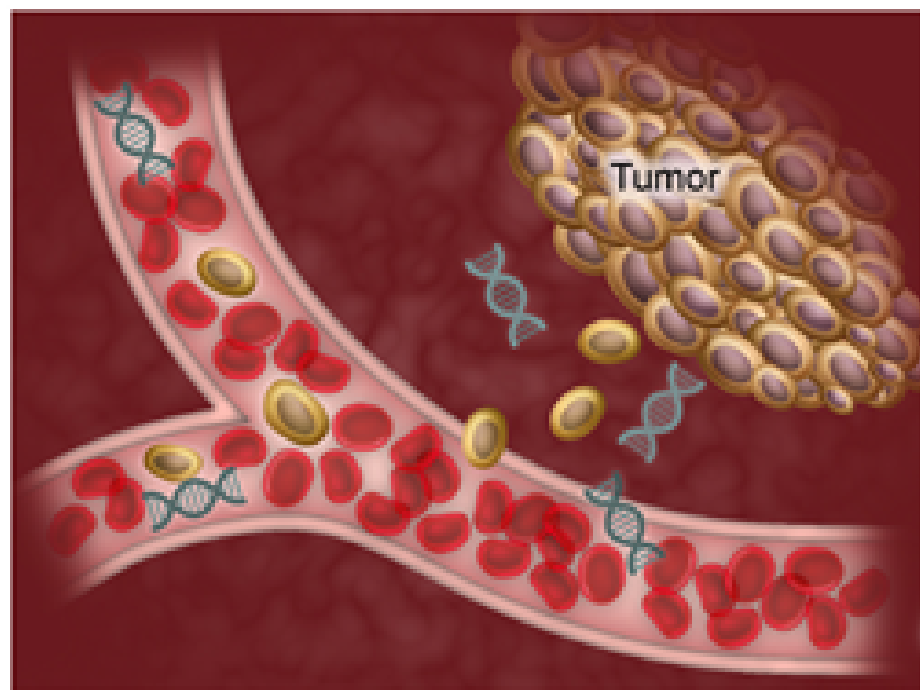
Journal of Clinical Oncology[®]
An American Society of Clinical Oncology Journal



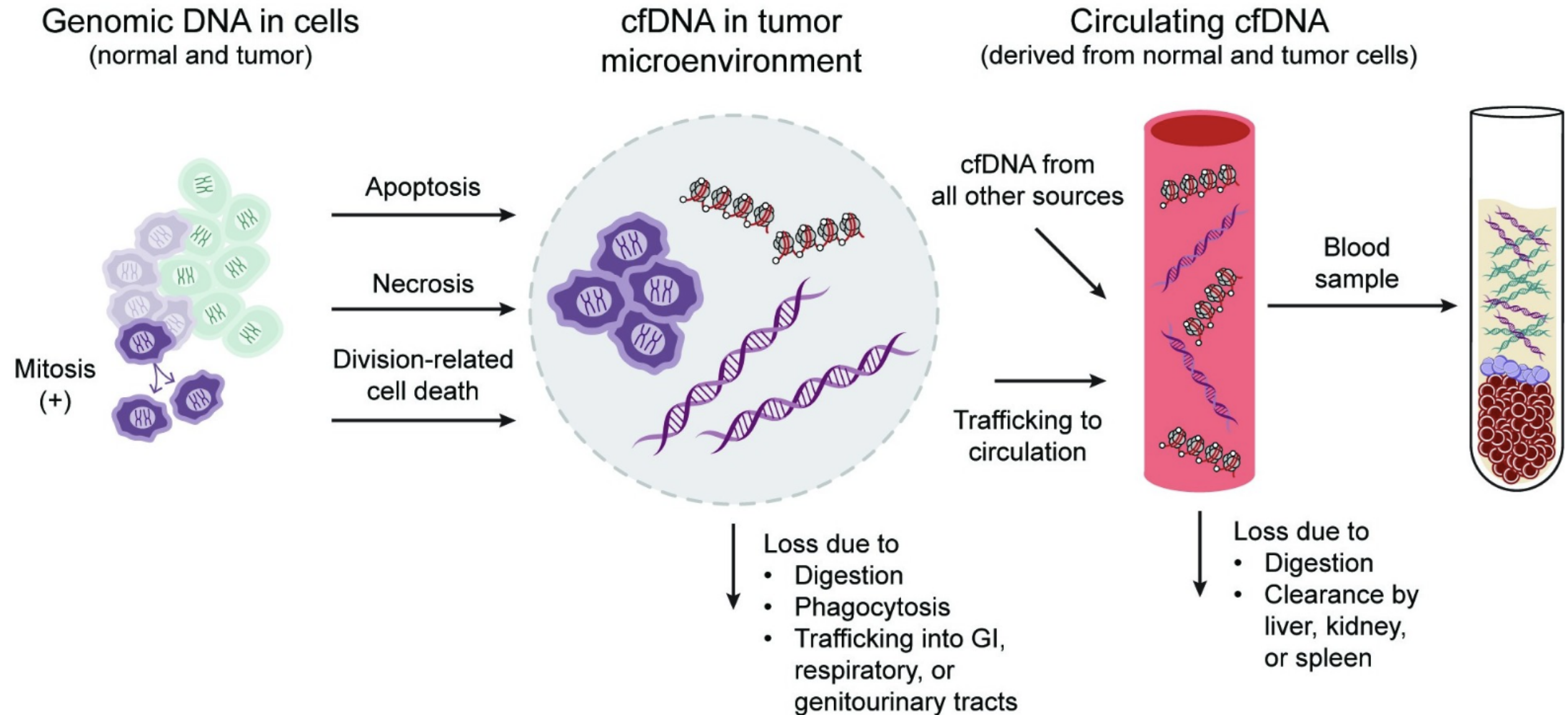
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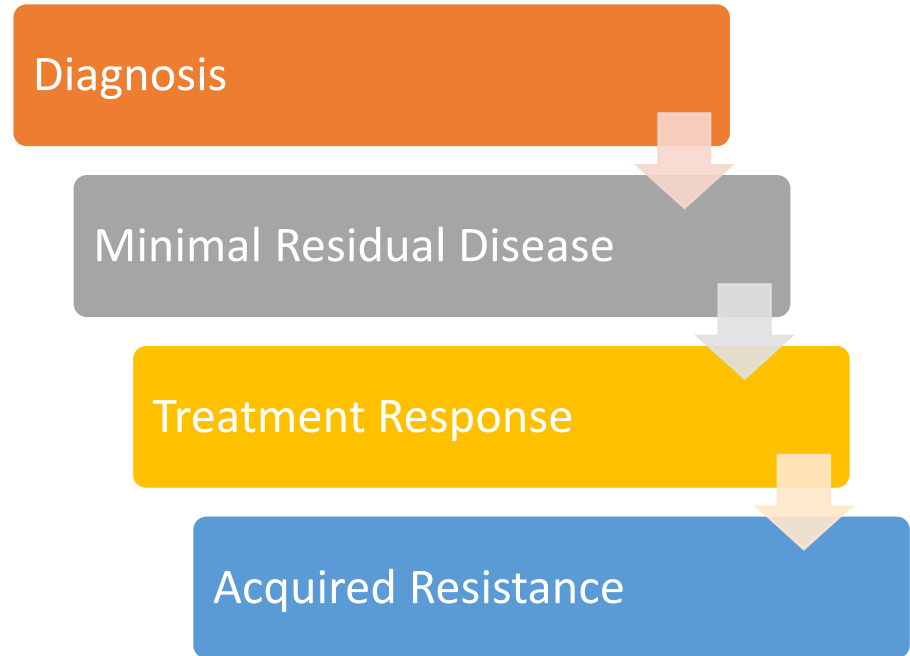
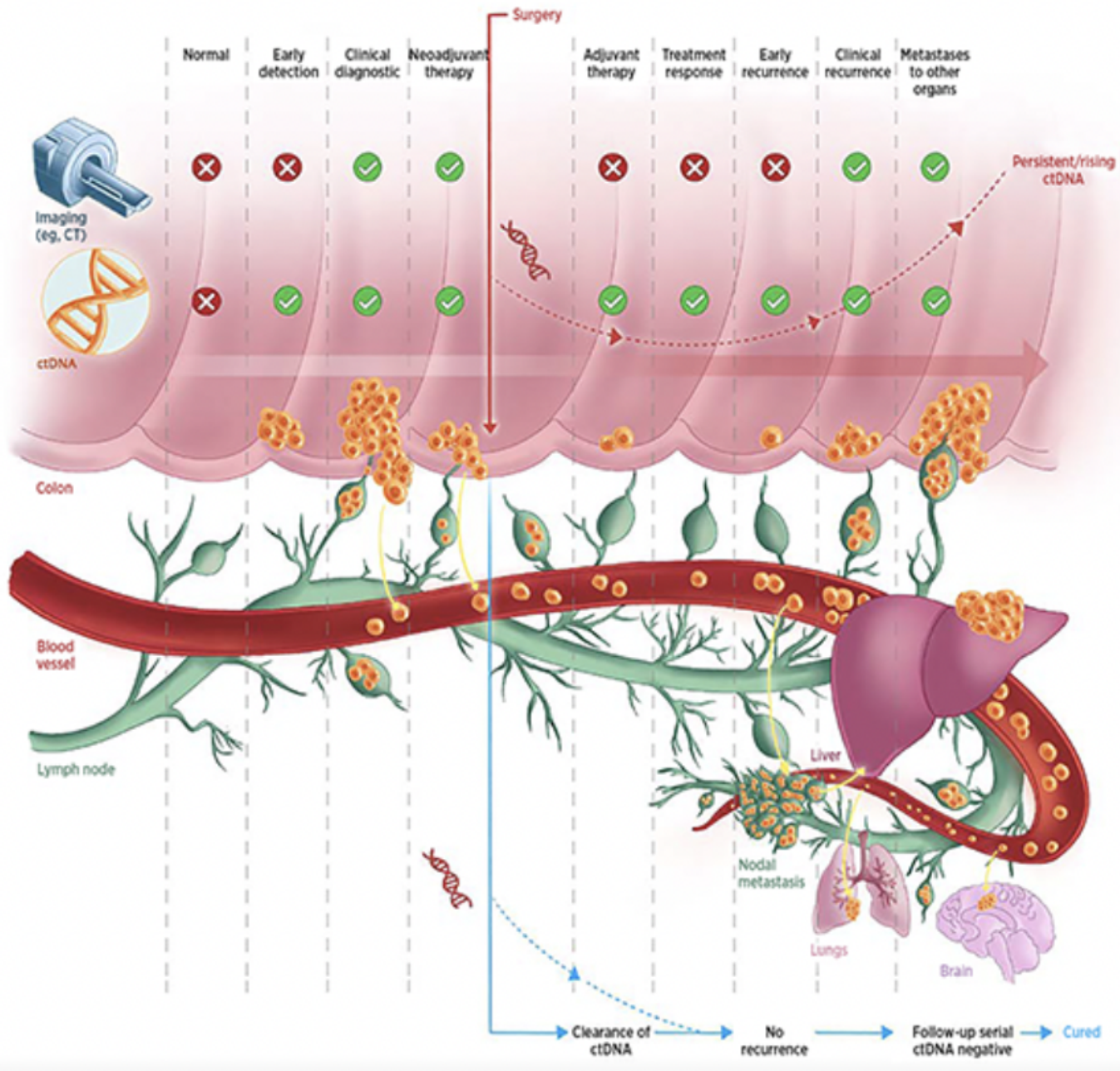
Liquid Biopsies (ctDNA) in Clinic for Colorectal Cancer





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





ASCO Daily News®

1

ctDNA – liquid biopsies for genotyping

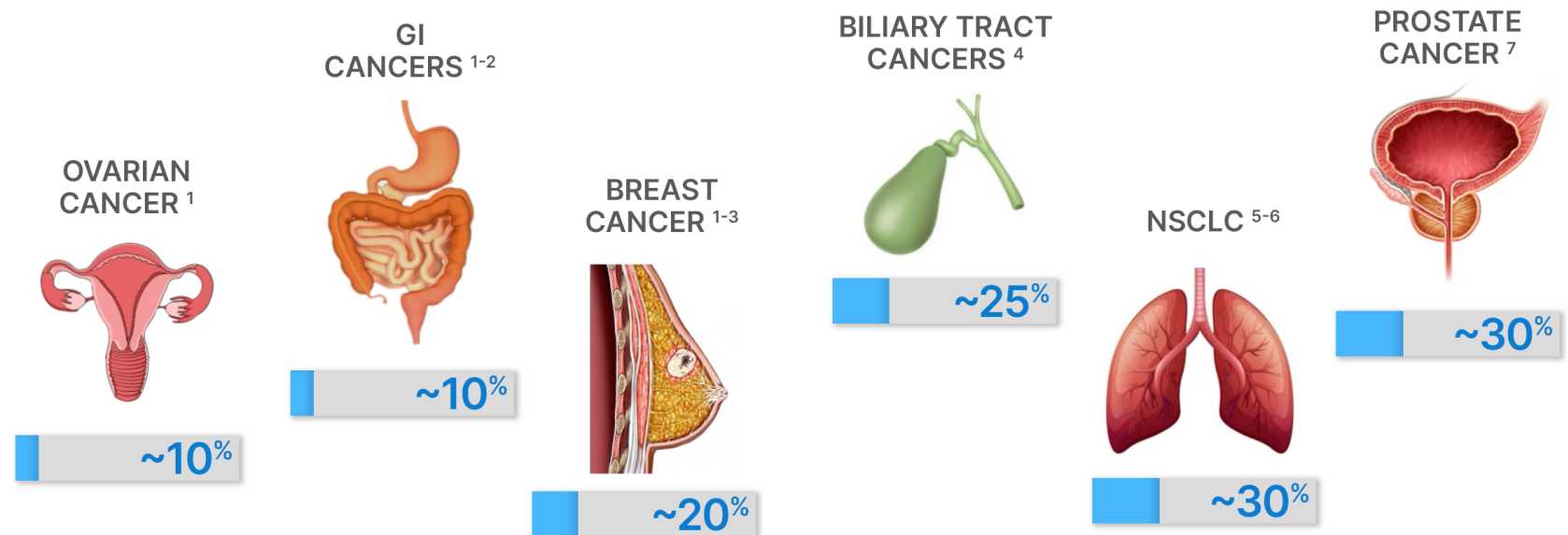
- “Blood-based Next Generation Sequencing (NGS) panels for determination of RAS/RAF-status, HER2-amplification, and rare actionable mutations and fusions.”



Version 4. 2025.
Colon Cancer.

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

Frequency of tissue insufficiency



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, Kapacze 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

1st line Anti-EGFR therapy selection

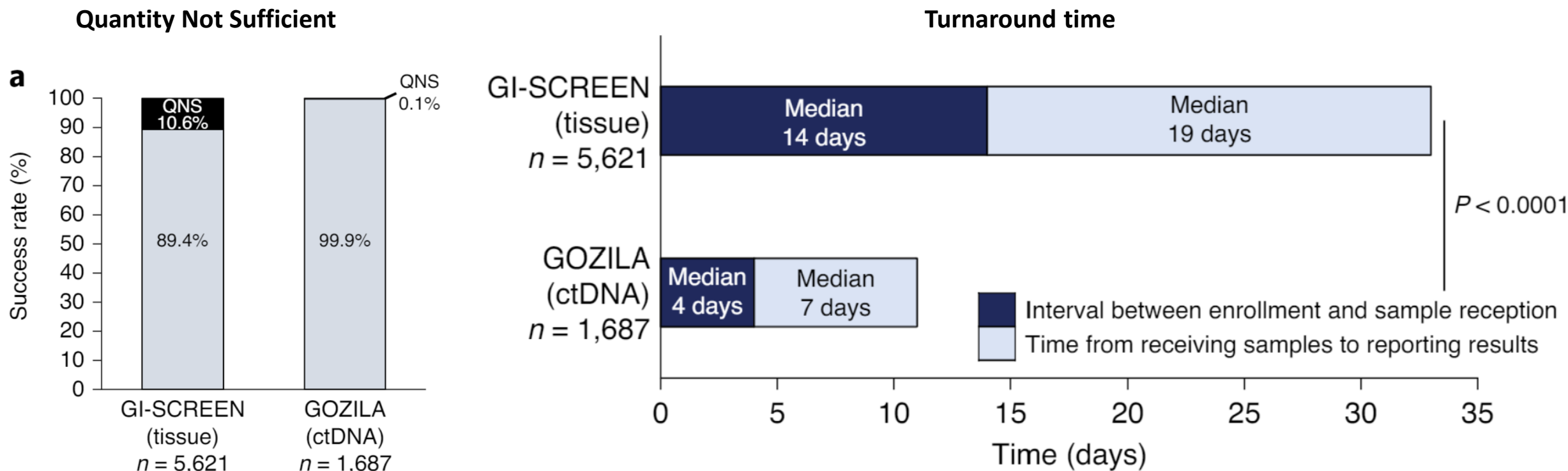
- **Selection** of the patient for anti-EGFR – tissue
 - LEFT
 - RAS-wildtype
 - BRAF-wildtype
 - HER2-negative
- Role for **liquid biopsies (YES)**

	<u>Anti-EGFR OS (months)</u>	<u>Anti-VEGF OS (months)</u>
NCDB	<u>42.9</u>	27.5
CALGB 80405	<u>39.3</u>	32.6
PEAK	<u>43.4</u>	32.0
FIRE-3	<u>38.3</u>	28.0
PARADIGM	<u>37.9</u>	34.7
PARADIGM (ctDNA hyper- selected)	<u>42.1</u>	35.5

1

Potential Advantages of Using ctDNA Assays to Assess Actionable Mutations

- Analysis of trial enrolment of patients with advanced GI cancers using ctDNA sequencing (GOZILA, $n = 1687$) vs tumor tissue sequencing (GI-SCREEN, $n = 5621$)



Turnaround time

RAS-testing and turnaround times

■ ≤5 days ■ ≤10 days ■ ≤14 days ■ 15 or more days

1

81%

≤14 days

≤10 days

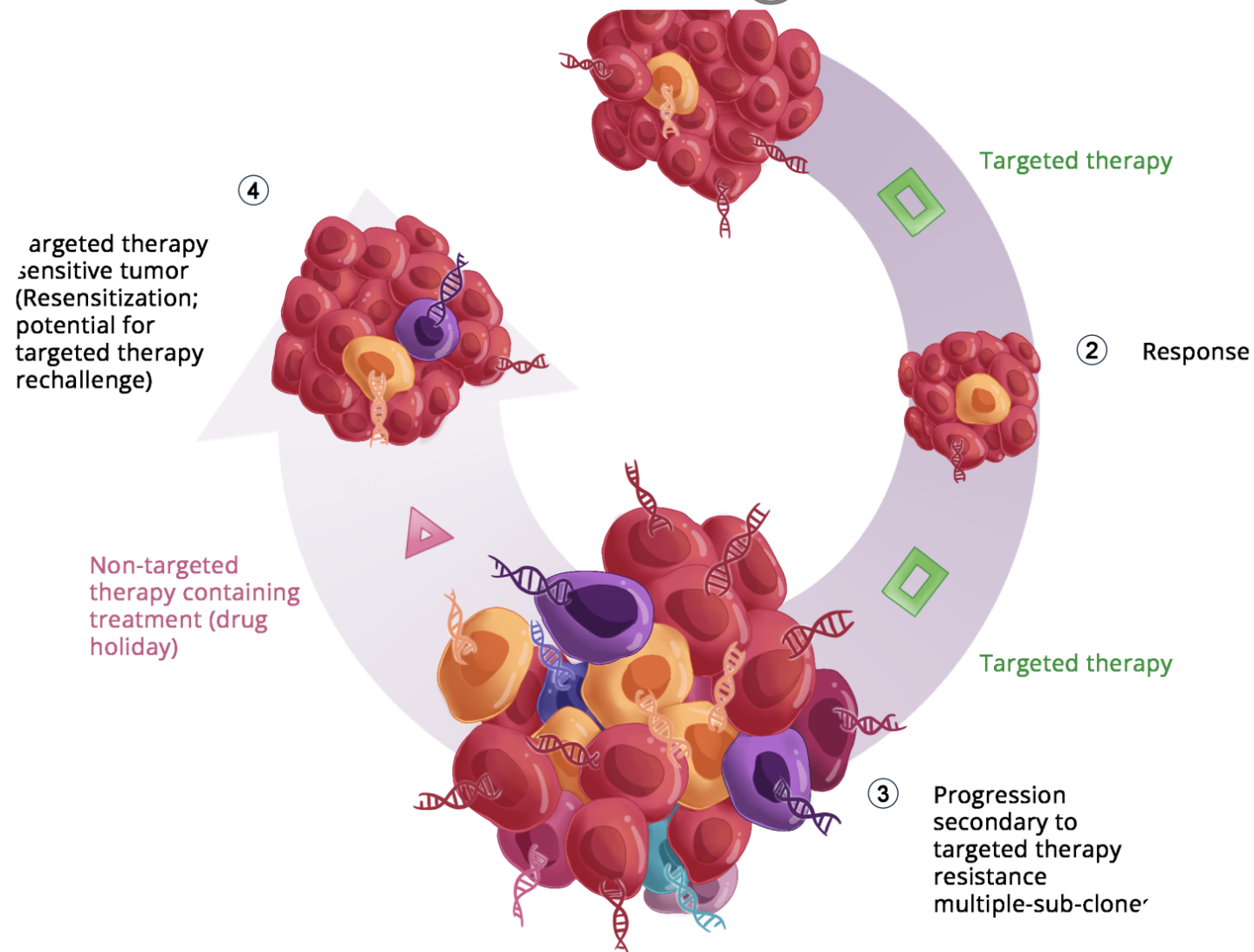
≤5 days

15 or more days

2

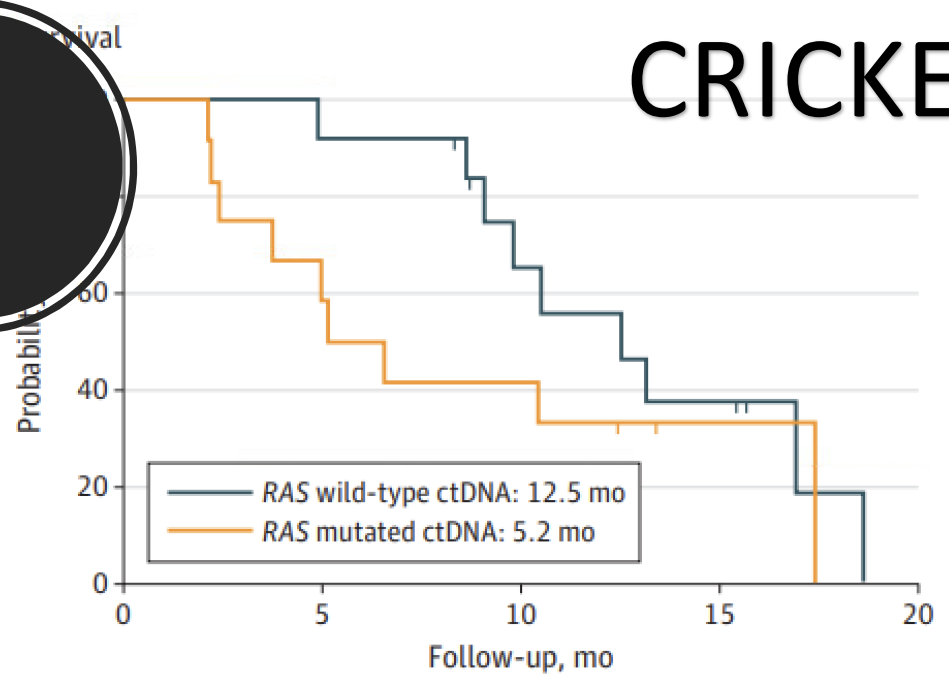
ctDNA – for EGFR-rechallenge

- Resensitization or Rechallenge for anti-EGFR therapy (cetuximab or panitumumab)

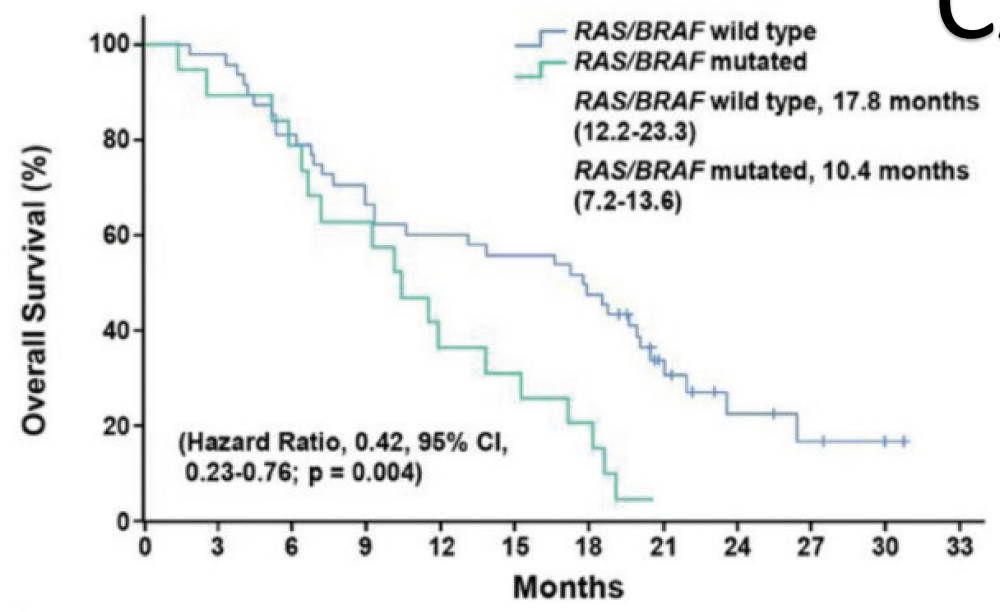


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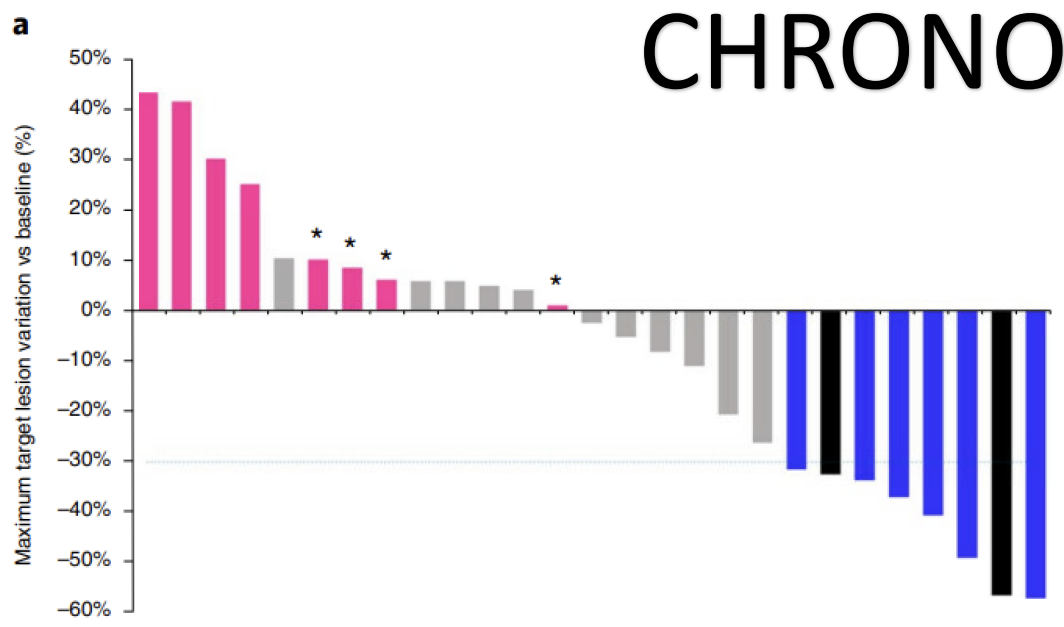
CRICKET



CAVE

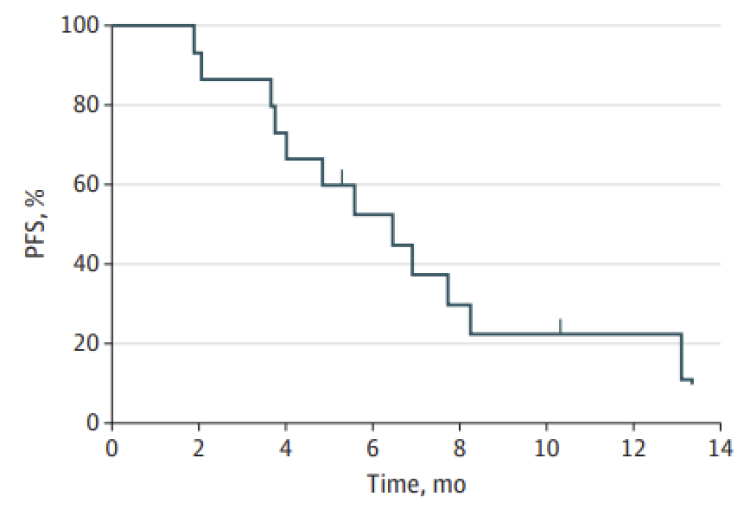


CHRONOS



VELO

Population with KRAS, NRAS, BRAFV600E, EGFR, ERBB2, MAP2K1, and PIK3CA WT ctDNA



3

ctDNA as a rapid surrogate of tumor response

ctDNA as a rapid surrogate of tumor response

- ctDNA clearance or decrease associated with progression-free survival and overall survival.



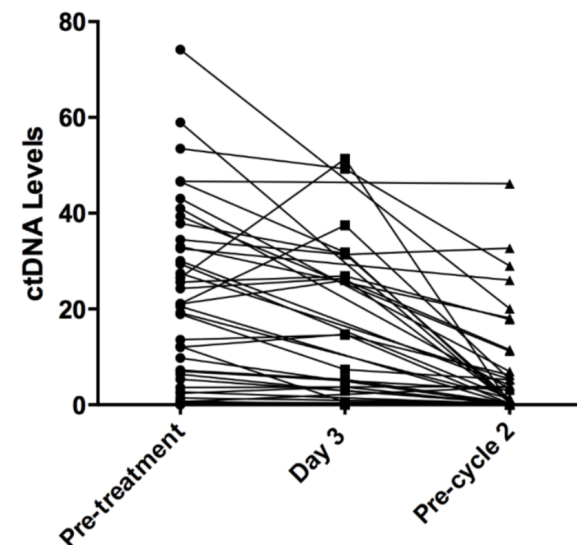
Half-life of ctDNA in circulation is measured in minutes/hours

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

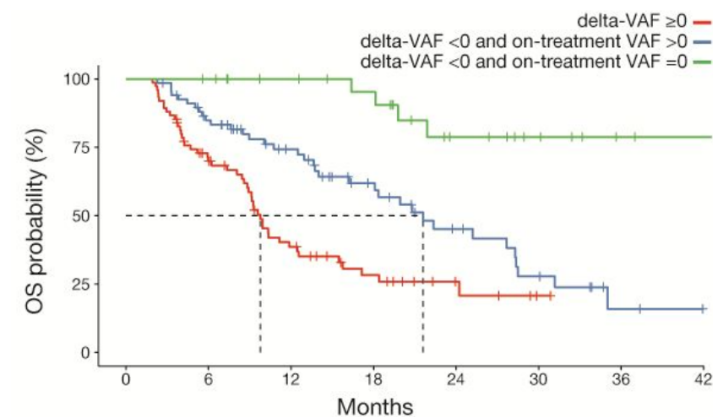
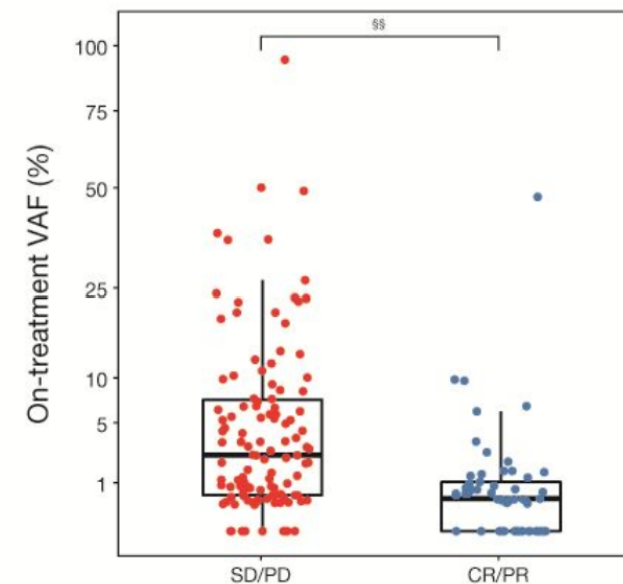
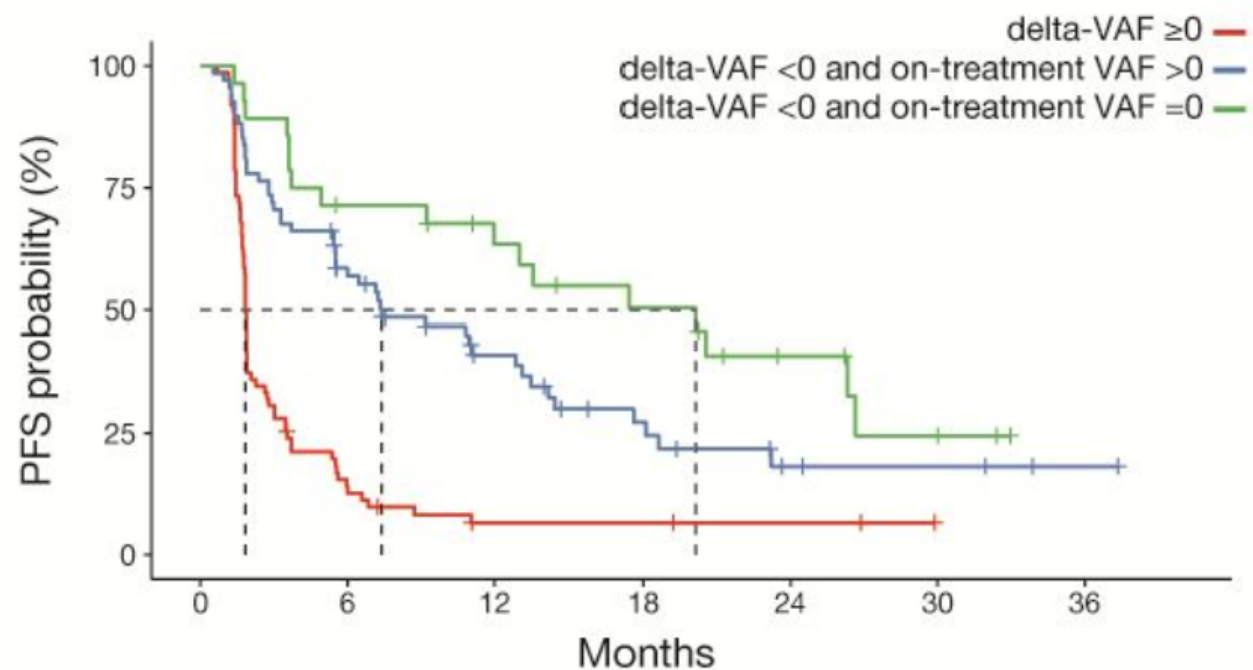


Timepoints Tie et al Annals Oncology '15

3

CANCER DISCOVERY

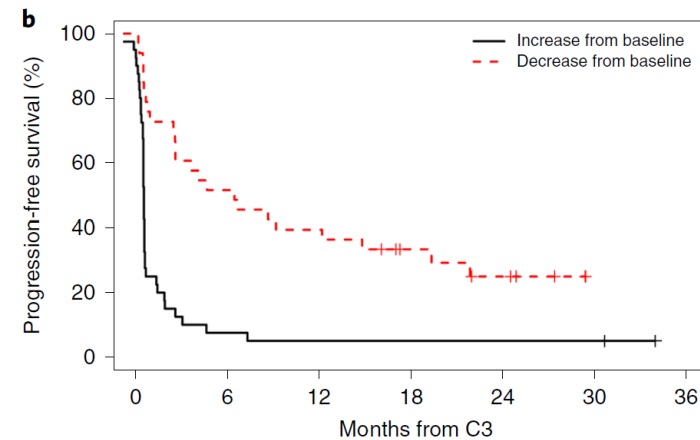
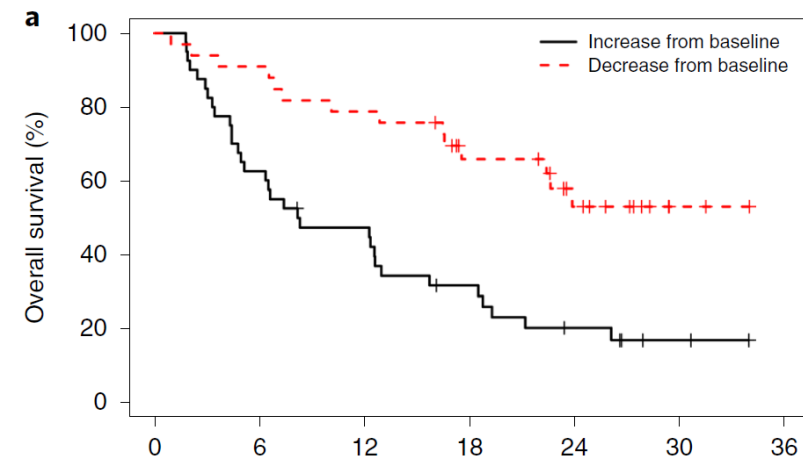
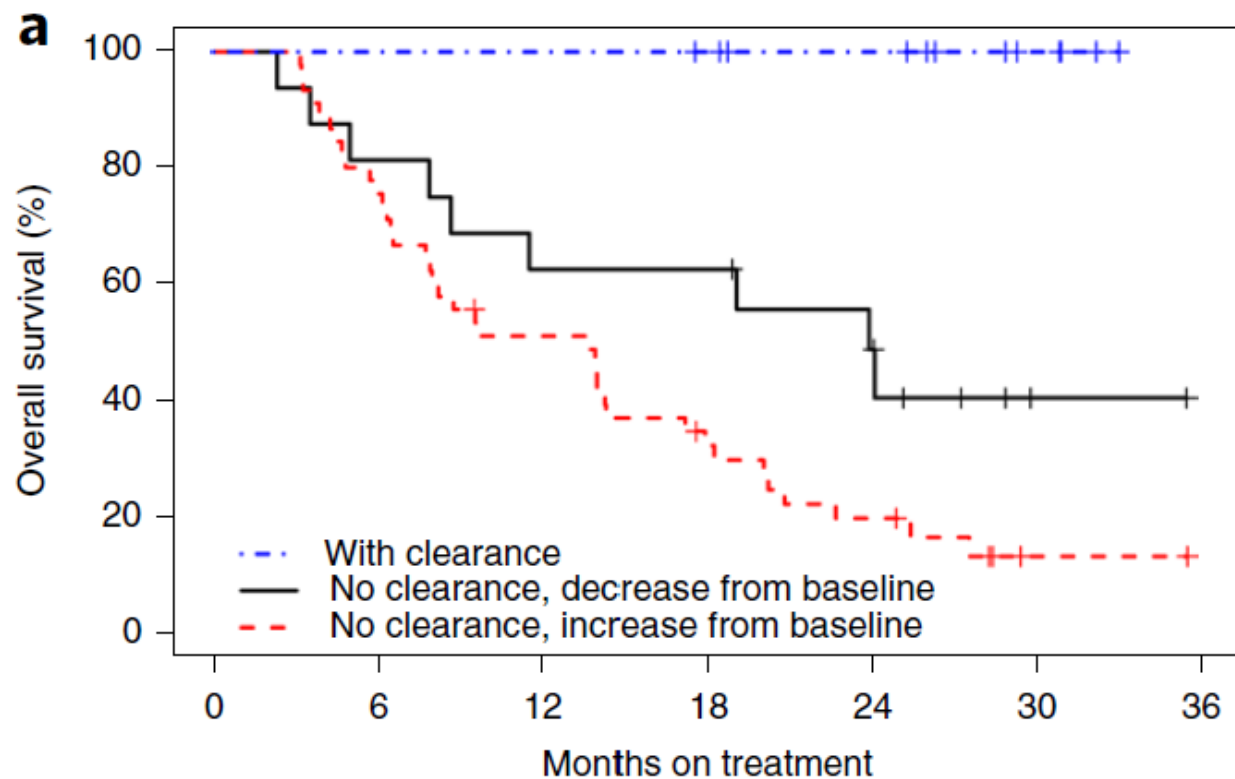
August 14, 2020



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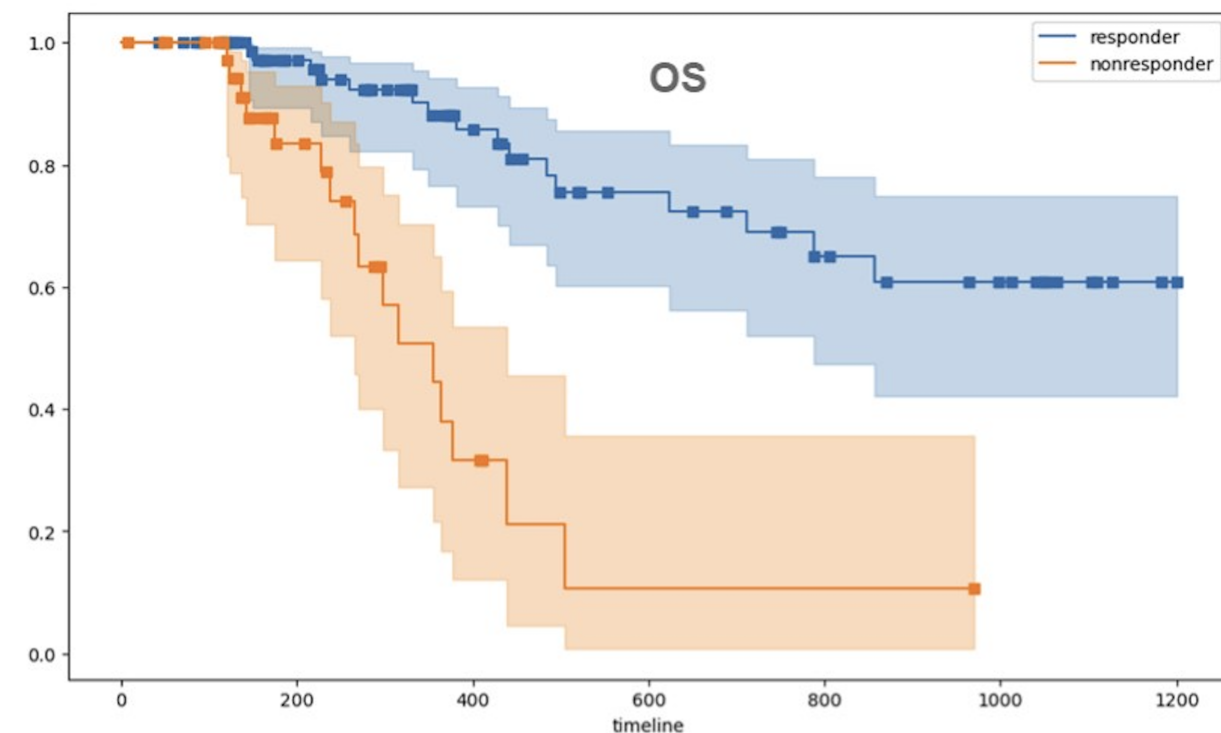
nature cancer

03 August 2020



3

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]

ASCO Daily News[®]

Kinetics of Liquid Biopsies in Predicting Response to Immunotherapy

October 1, 2020

Pashtoon M. Kasi, MD, MS

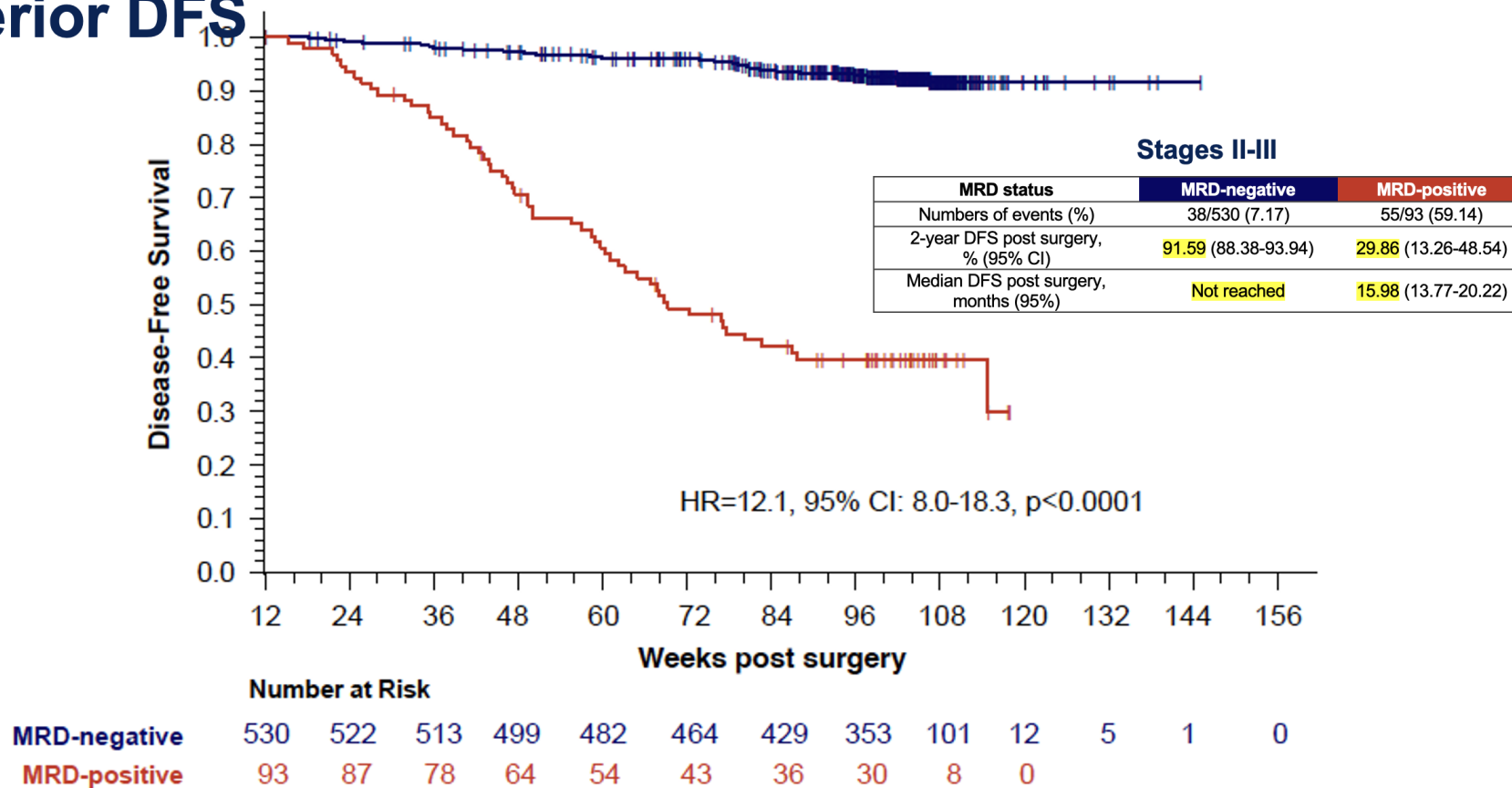
 @pashtoonkasi

4

ctDNA for minimal residual disease assessment

ctDNA-positivity at MRD time point is predictive of inferior DFS

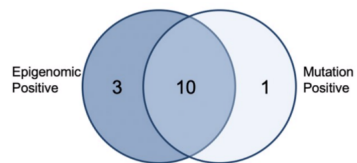
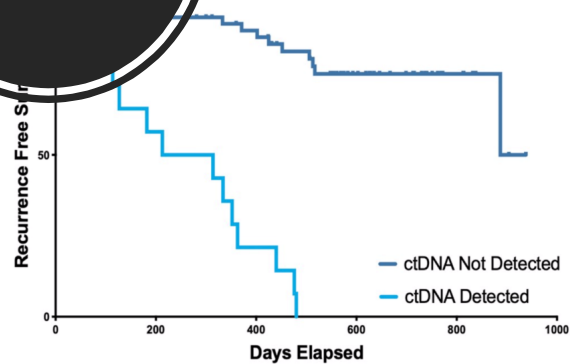
- ctDNA has emerged as the strongest predictor of disease free and overall survival.



4

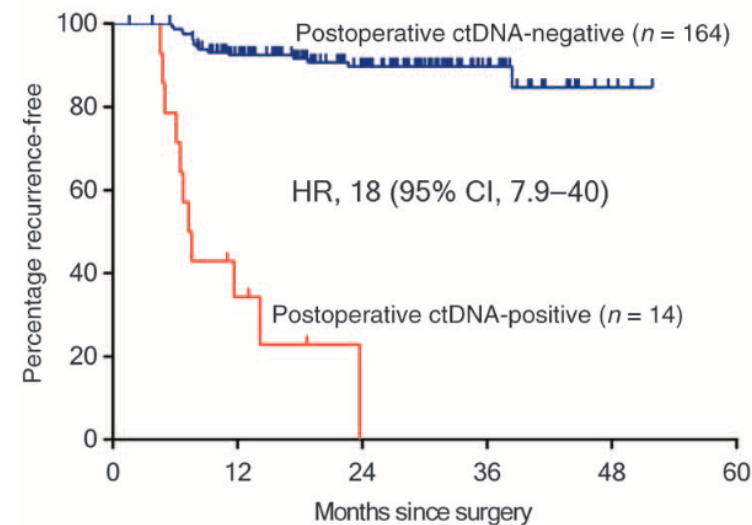
Prediction of relapse post-SOC in CRC

Post-Completion of Standard of Care Therapy



Assay Performance by Analysis		
	Genomic (N)	Integrated Genomic and Epigenomic (N)
PPV (N of patients with ctDNA detected who recurred)	100% (11 / 11)	100% (14 / 14)
NPV (N of patients with ctDNA not detected who were recurrence free)	72% (42 / 58)	76% (42 / 55)
Sensitivity for recurrence within one year of surgery	56% (9 / 16)	69% (11 / 16)
Specificity for recurrence within one year of surgery	96% (51 / 53)	94% (50 / 53)

A All no-chemo patients

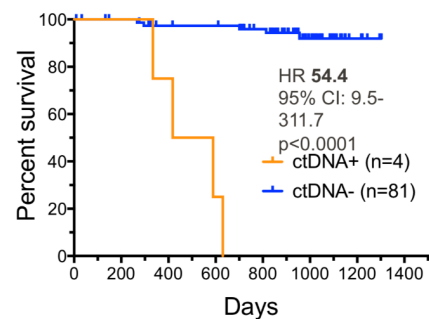


NGS Assay

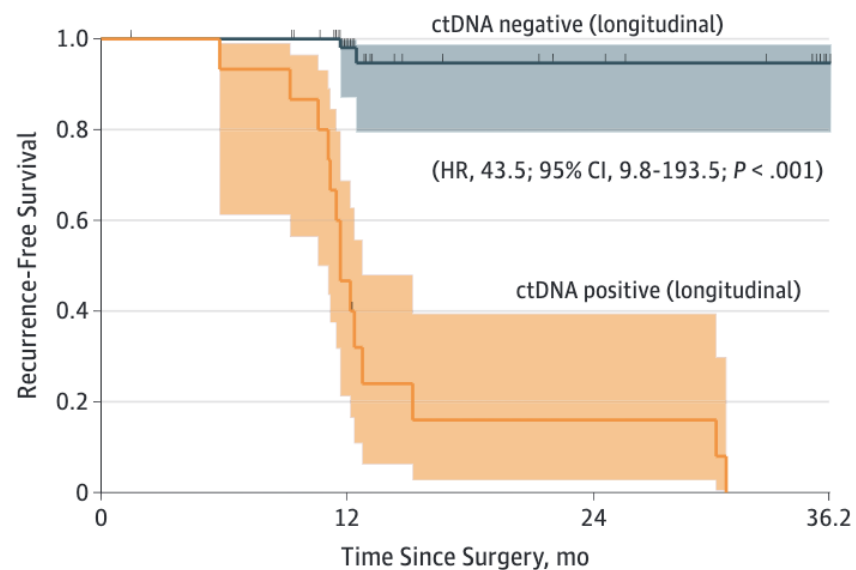
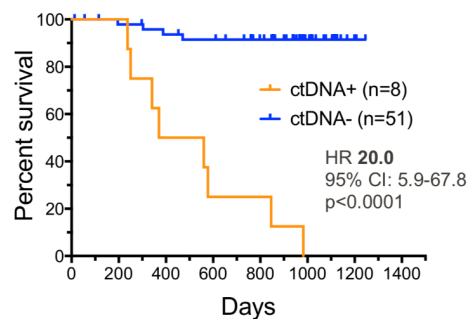
Assay with 197 genes; at least one mutation detected 99.3% of tumor tissue

57% sensitivity for recurrence; 100% specificity

Stage II (5% prevalence of ctDNA+)



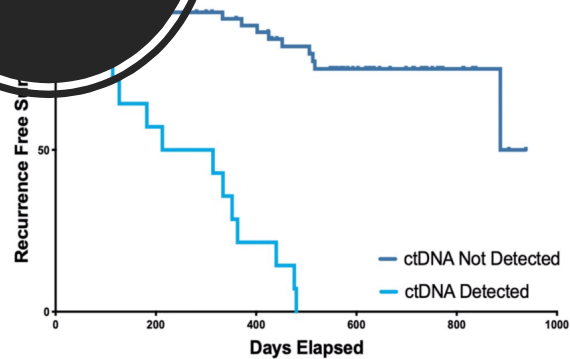
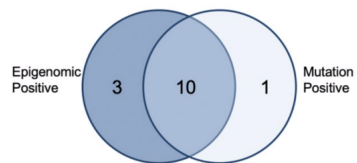
Stage III (16% prevalence of ctDNA+)



4

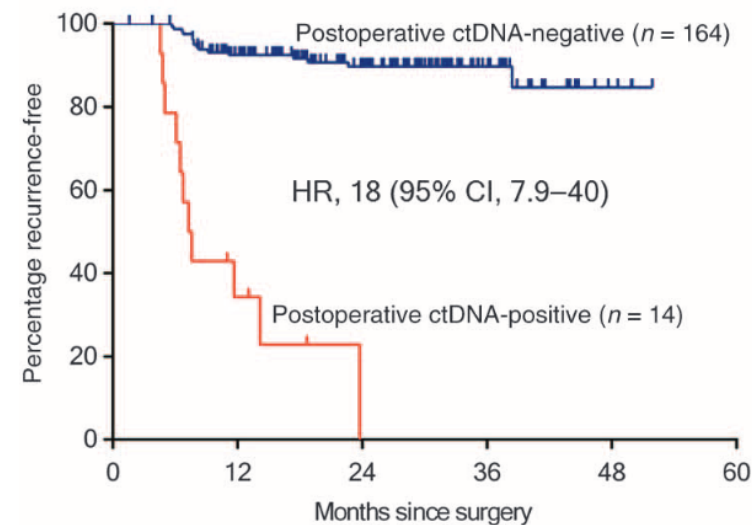
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A All no-chemo patients



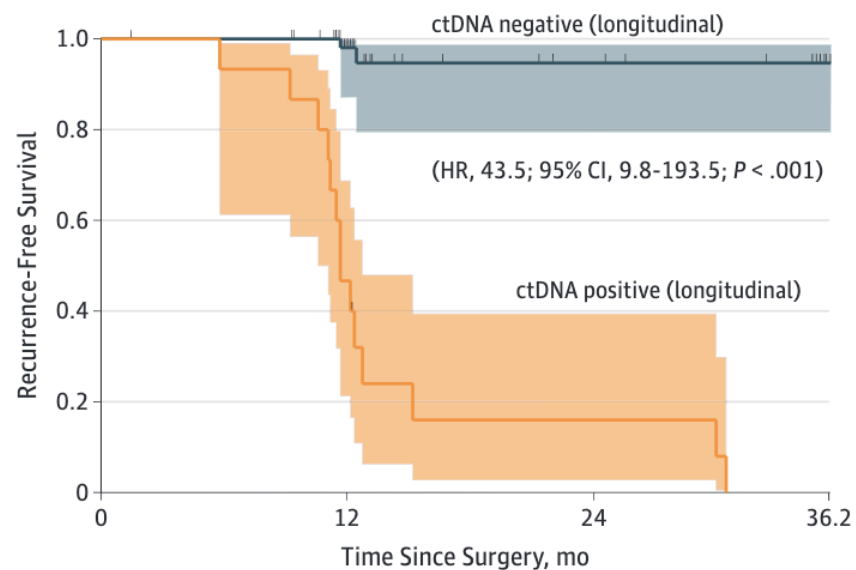
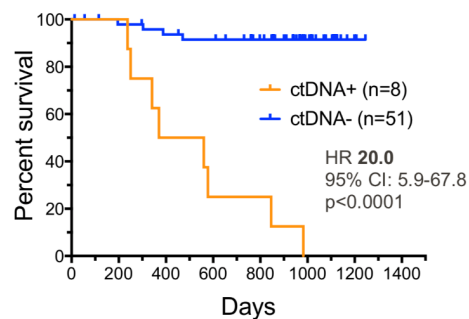
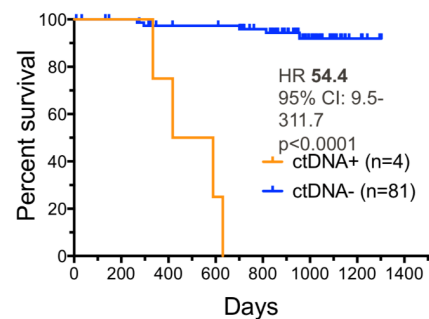
NGS Assay (Roche Molecular)

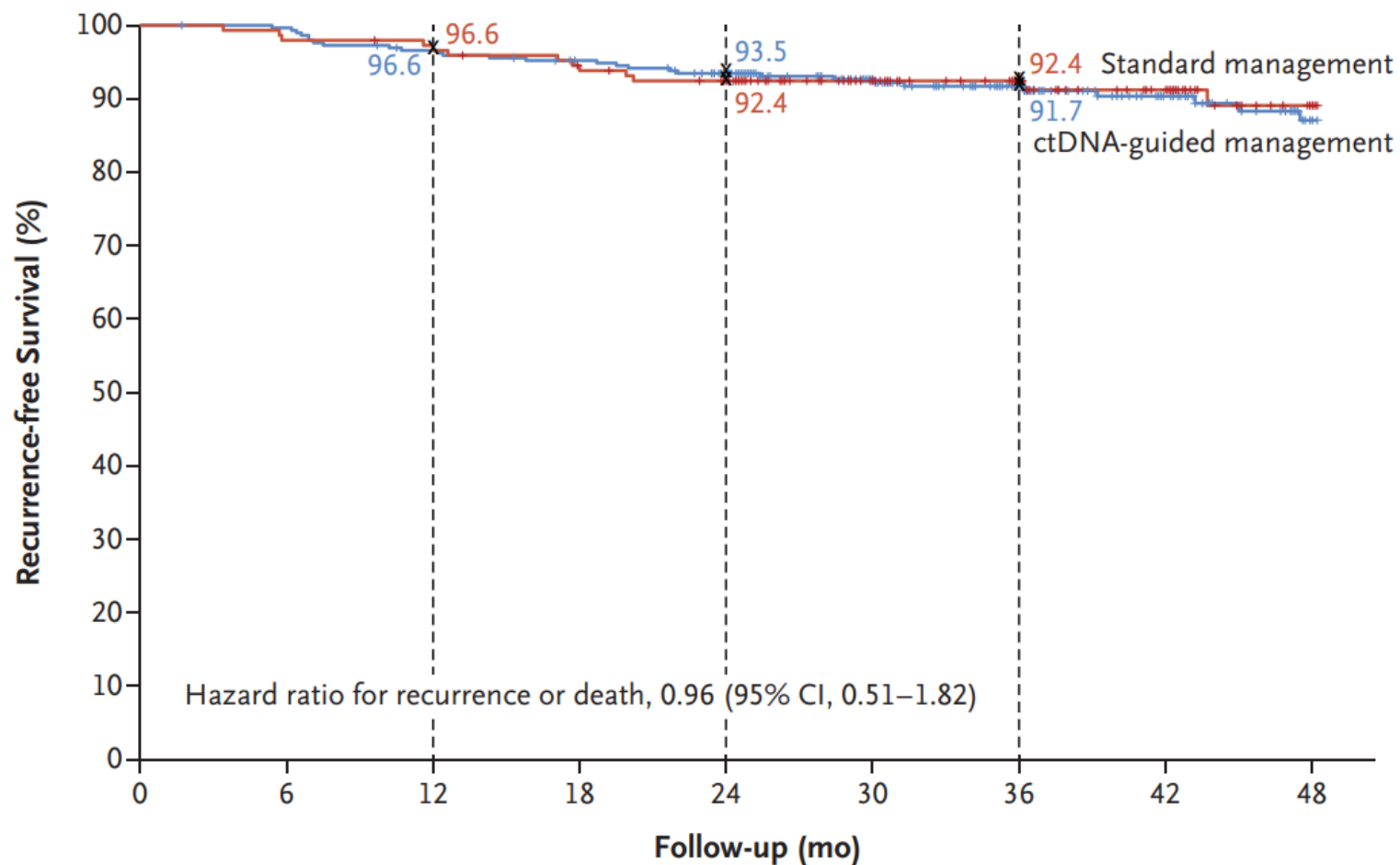
Assay with 197 genes; at least one mutation detected 99.3% of tumor tissue

57% sensitivity for recurrence; 100% specificity

Stage II (5% prevalence of ctDNA+)

Stage III (16% prevalence of ctDNA+)



B Kaplan–Meier Estimates of Recurrence-free Survival

The NEW ENGLAND
JOURNAL of MEDICINE

Tie et al. June 16, 2022

N Engl J Med 2022; 386:2261-2272

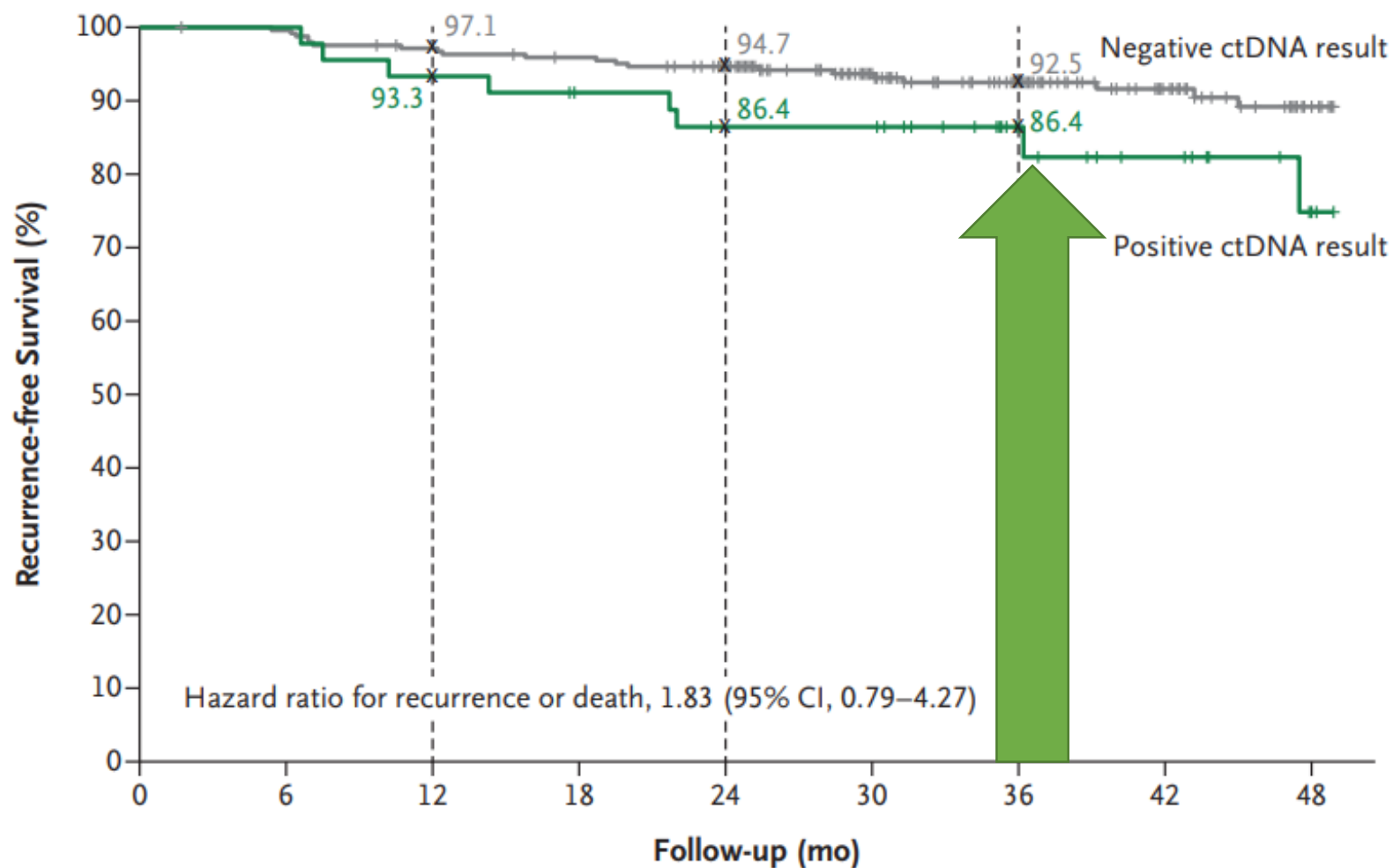
No. at Risk

Standard management	147	144	142	136	128	97	78	57	33
ctDNA-guided management	294	292	281	273	259	207	155	109	64



The NEW ENGLAND
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Tie et al. June 16, 2022
N Engl J Med 2022; 386:2261-2272



No. at Risk

Negative ctDNA result

246

244

236

231

220

169

131

93

55

Positive ctDNA result

45

45

42

39

36

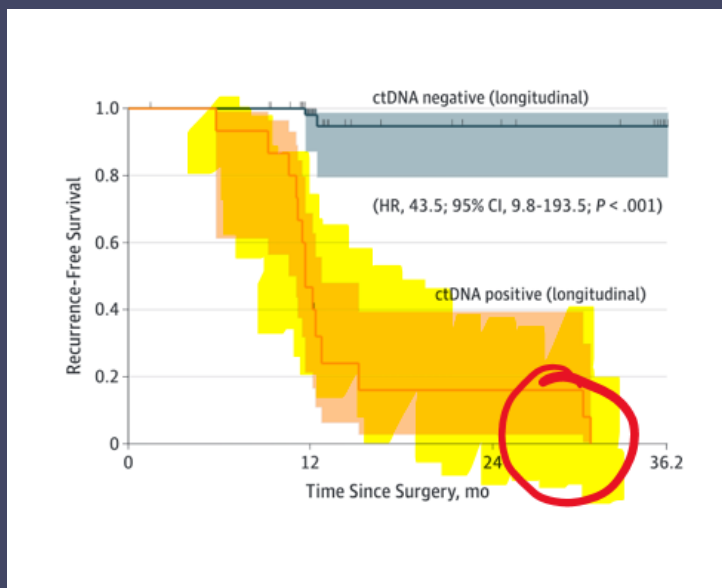
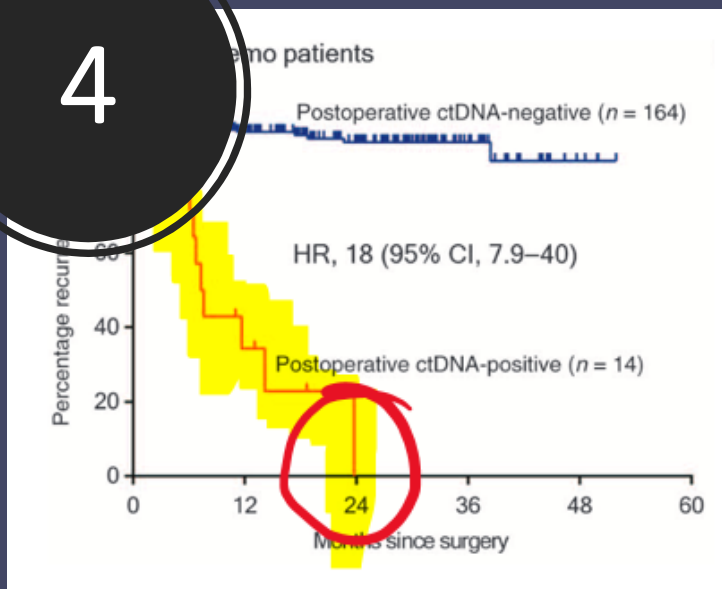
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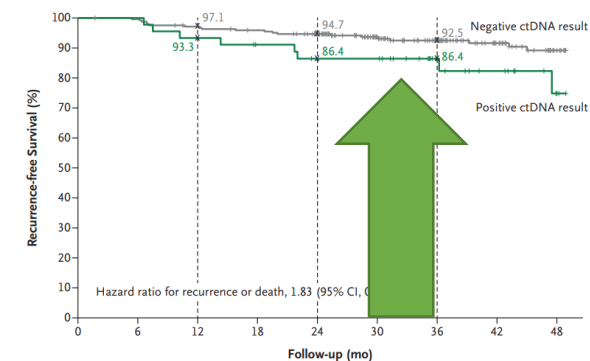
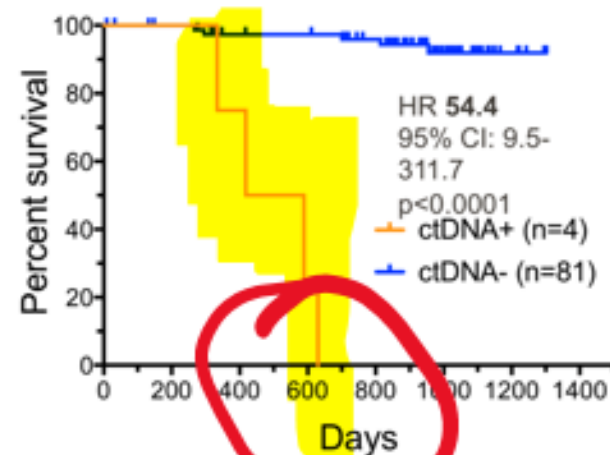
16

9

4



Stage II (5% prevalence of ctDNA+)



No. at Risk

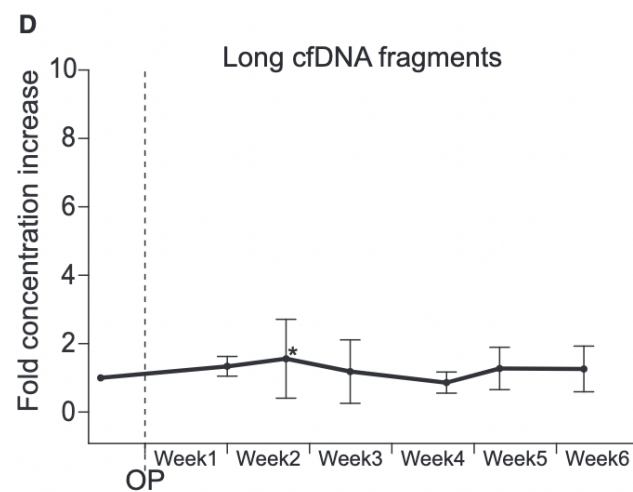
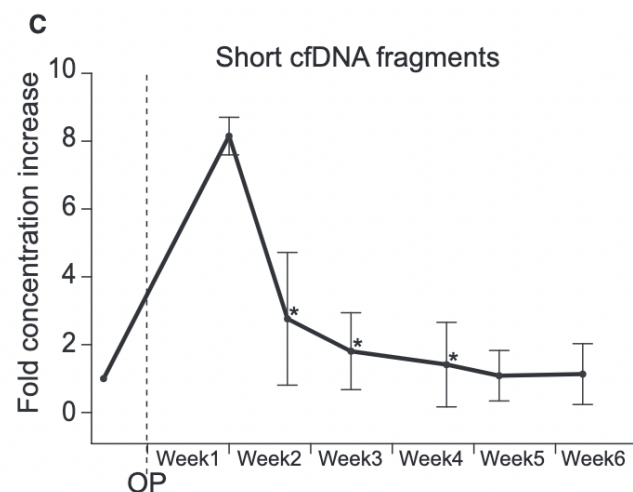
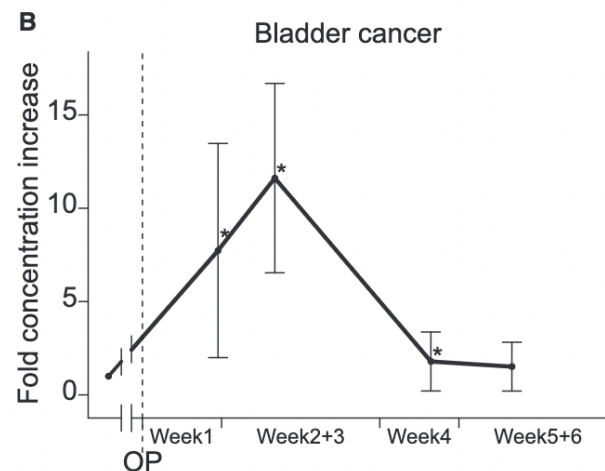
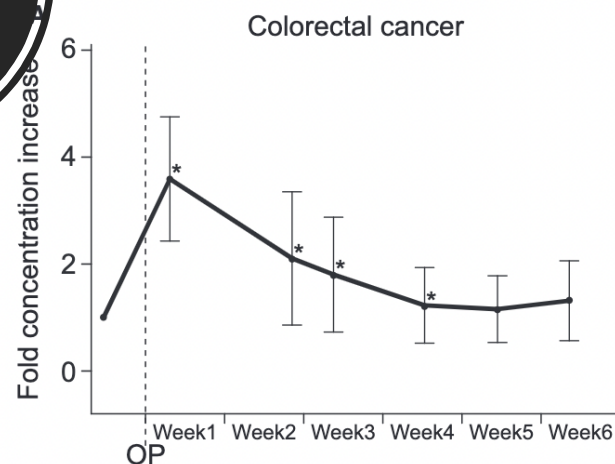
Negative ctDNA result

Positive ctDNA result



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Tie et al. June 16, 2022
N Engl J Med 2022; 386:2261-2272



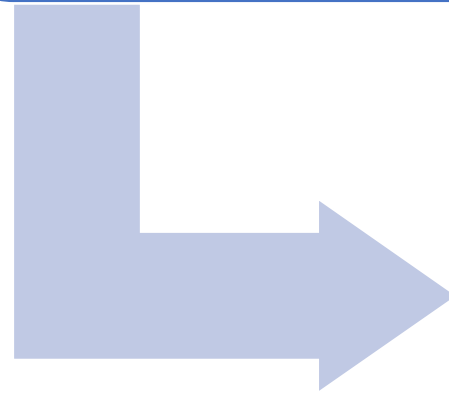
Surgical
trauma
induced
cfDNA affects
ctDNA
detection

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.

4

Timing is key

Finding the
needle in the
haystack



Immediate post-
operative period
– bigger
haystack



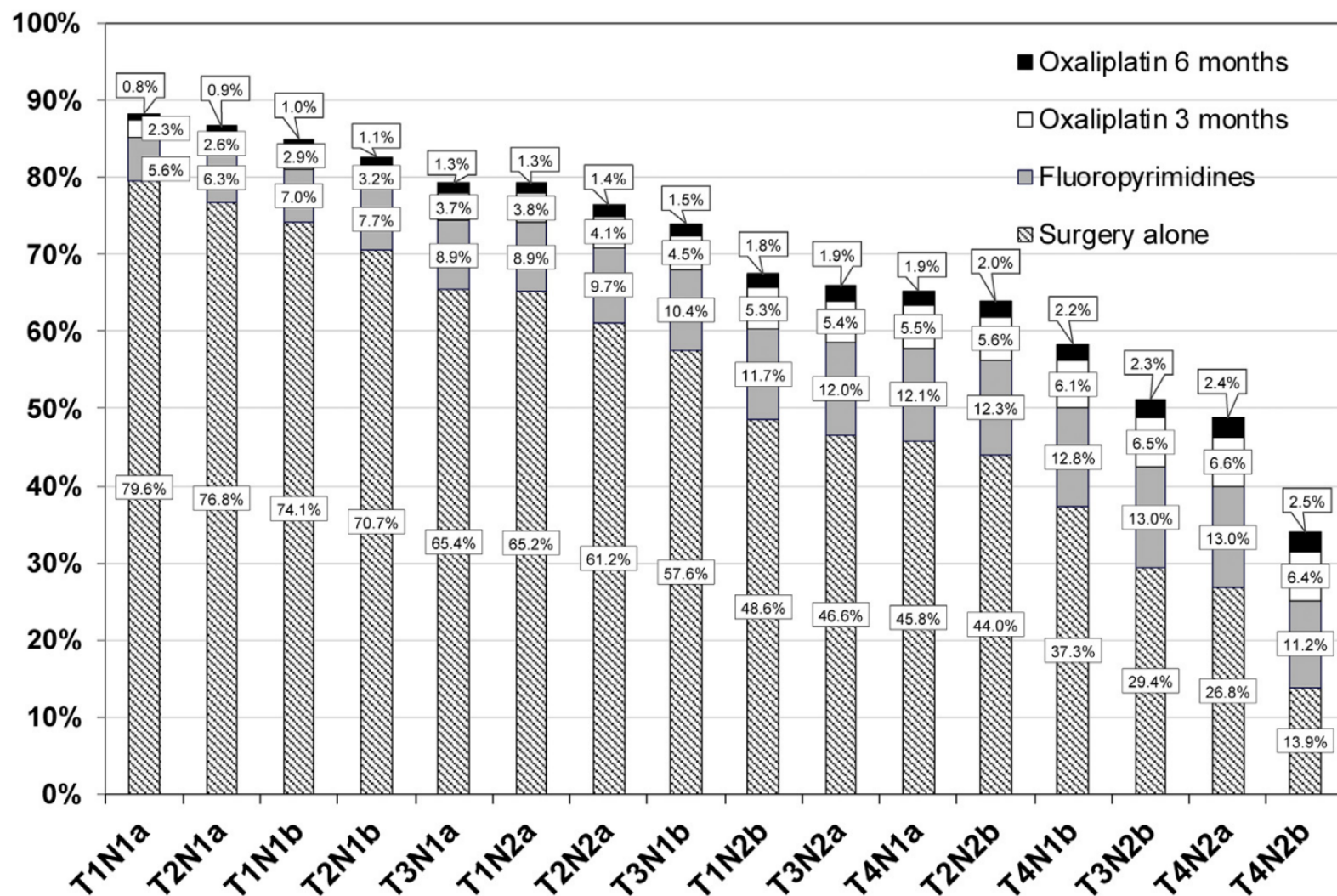


Fig. 2. Predicted 5-year DFS in the 16 prognostic sub-stages within stage III treated with surgery alone (dashed bar, HR = 0.7); fluoropyrimidine alone (light grey bar, HR = 0.78); oxaliplatin-based doublet for 3 months (white bar, HR = 0.93), oxaliplatin-based doublet for 6 months (black bar).

4



T4

High risk

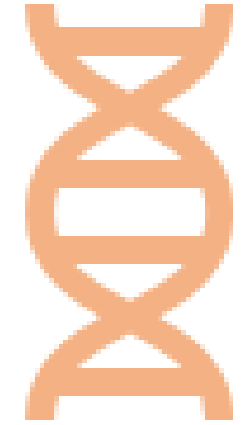
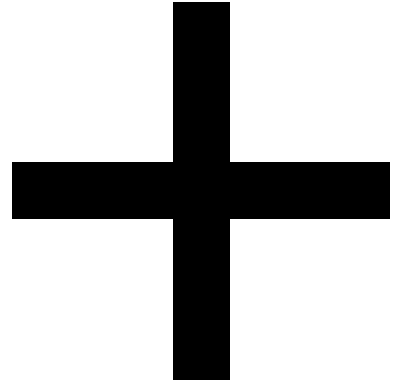
N2

Node positive

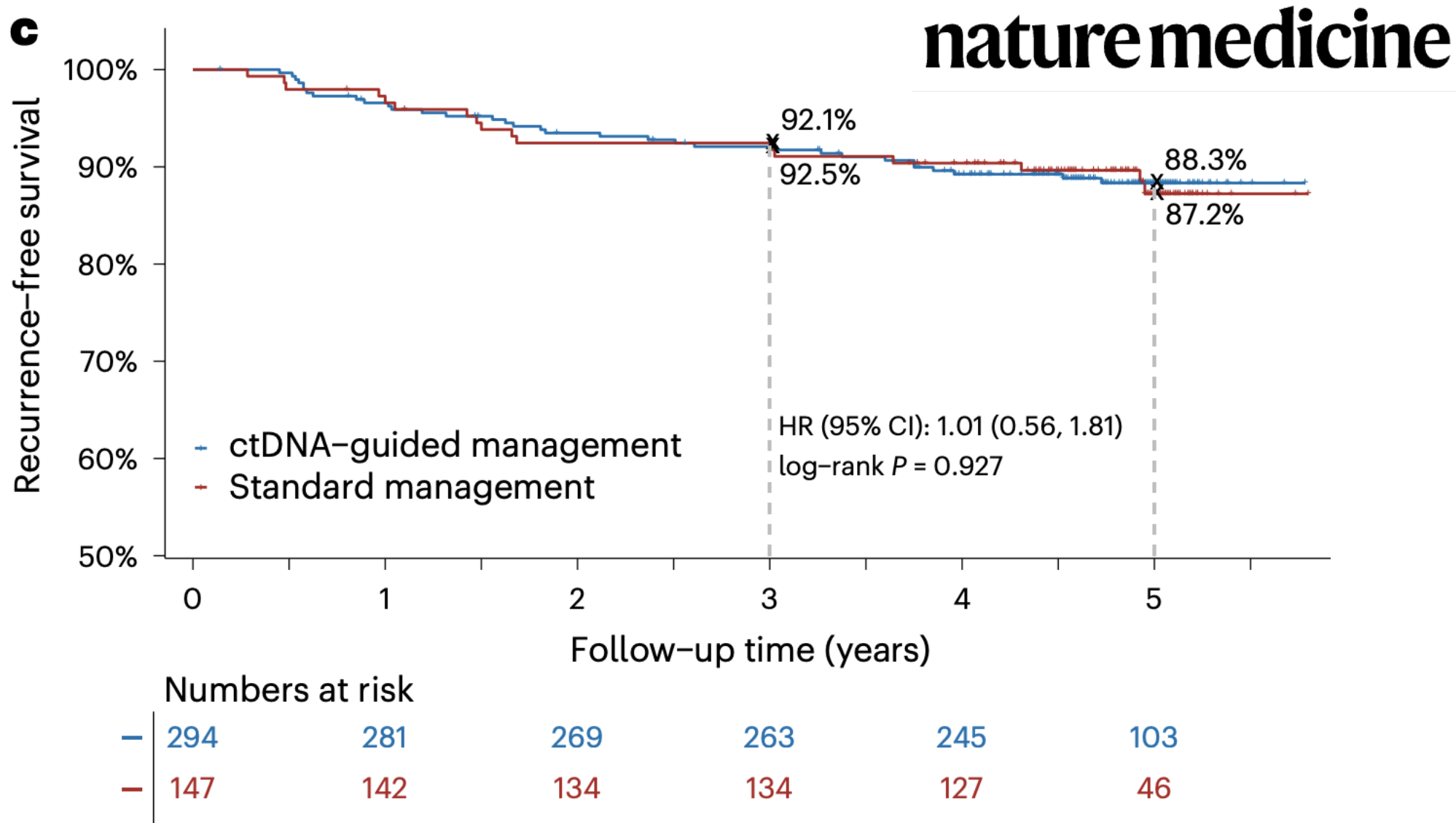


MSI-High

Mismatch repair deficiency

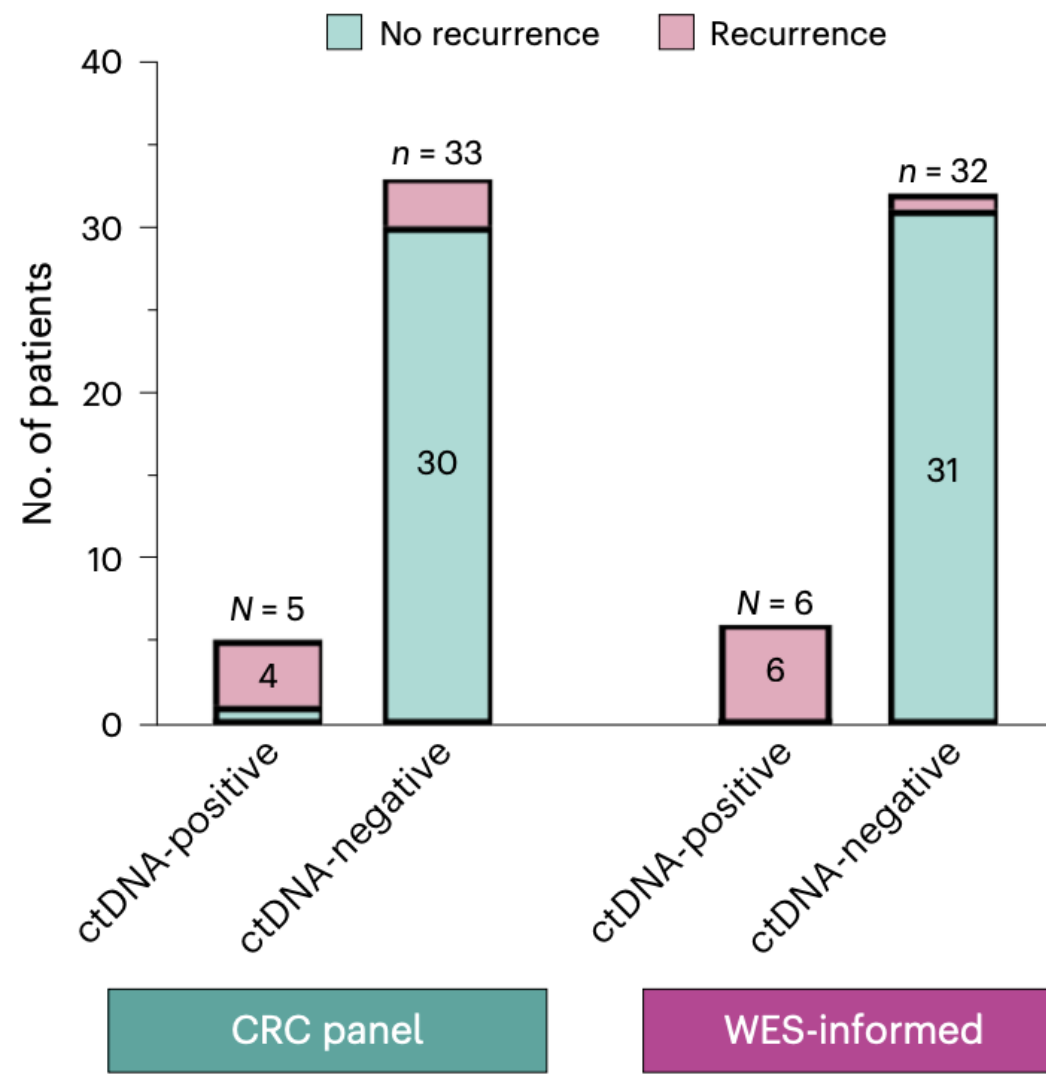
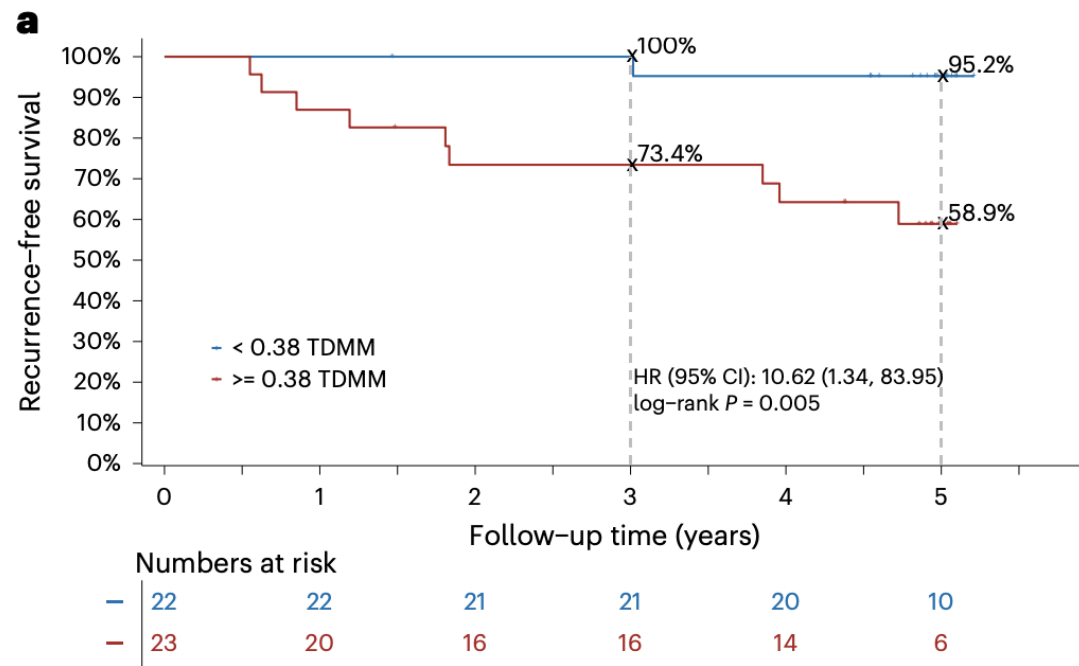


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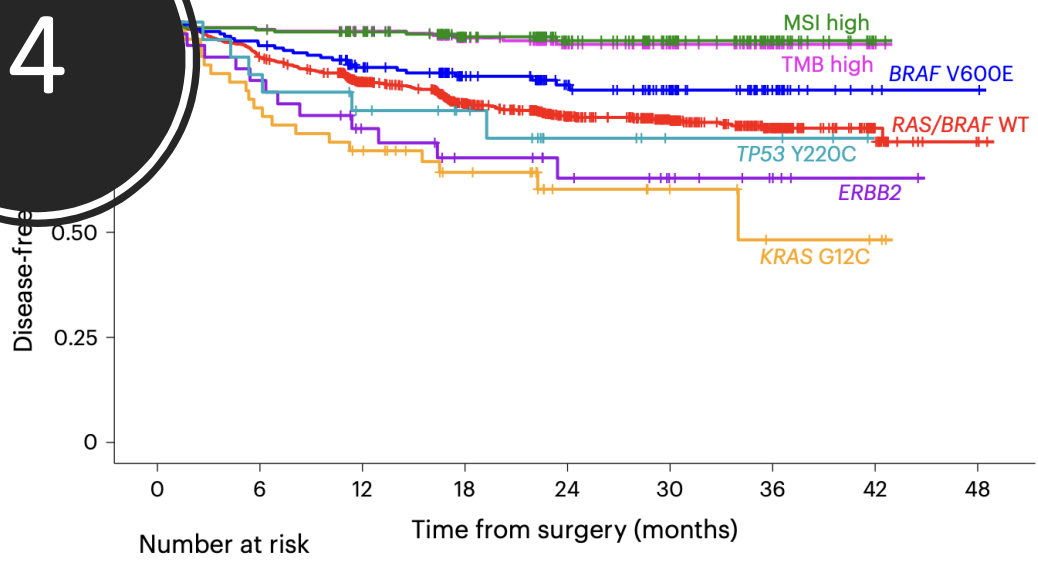


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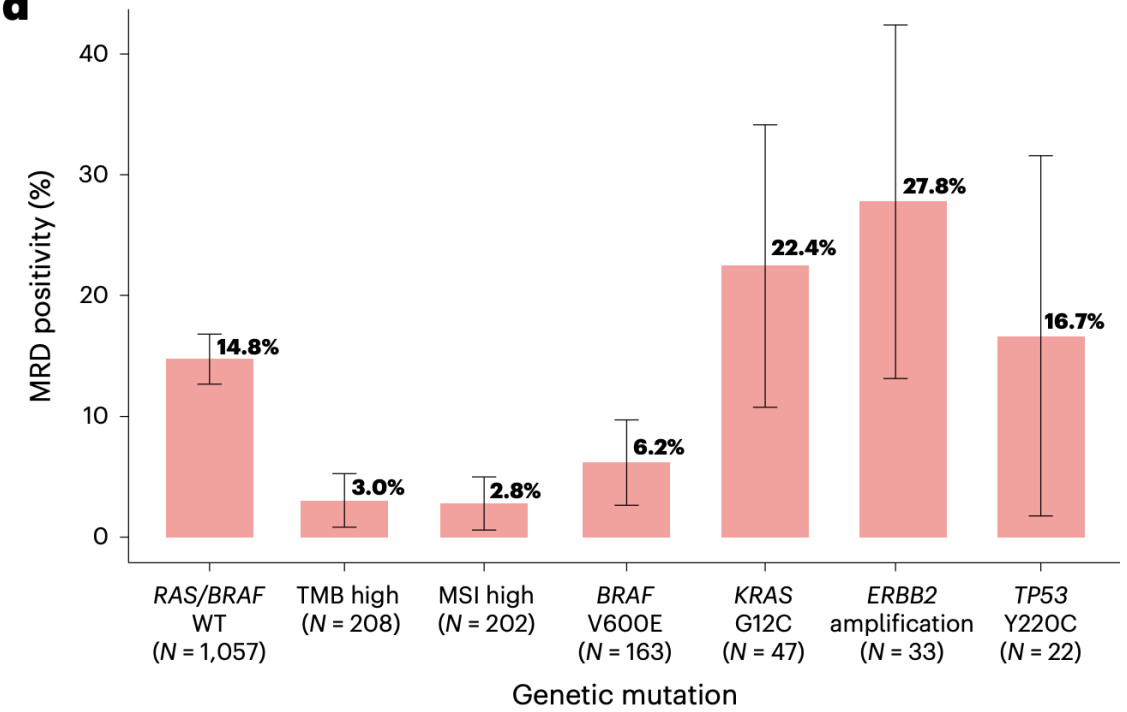
nature medicine



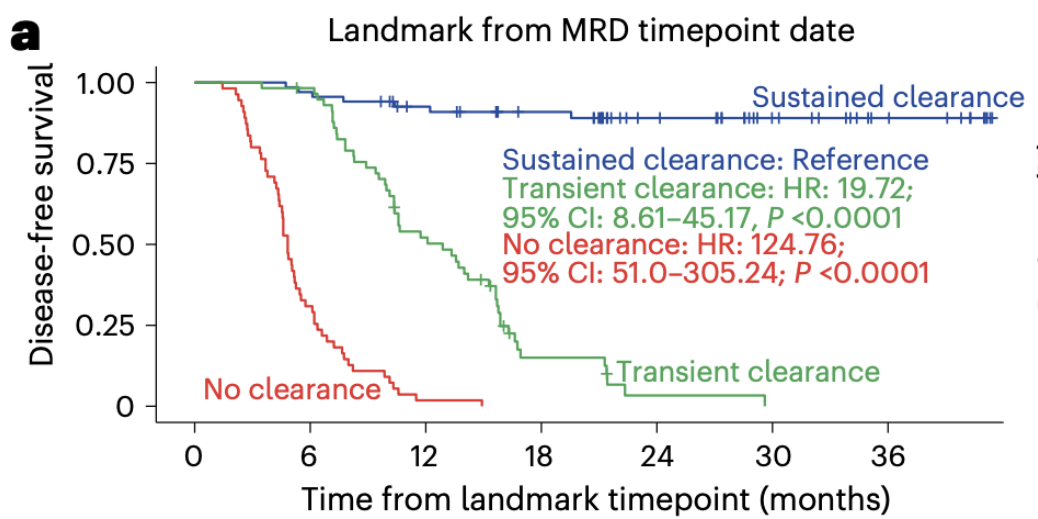
4



d



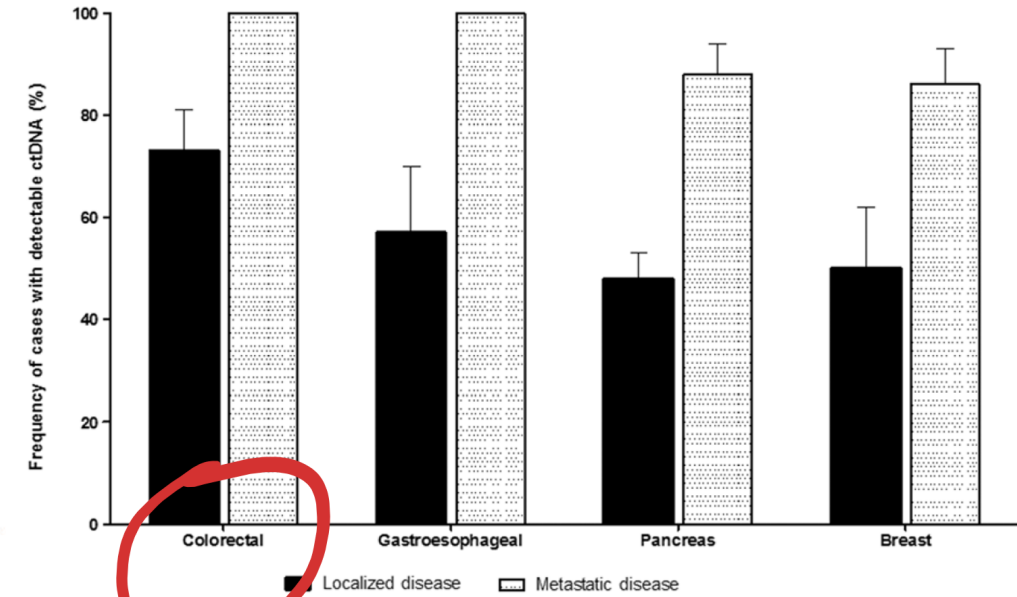
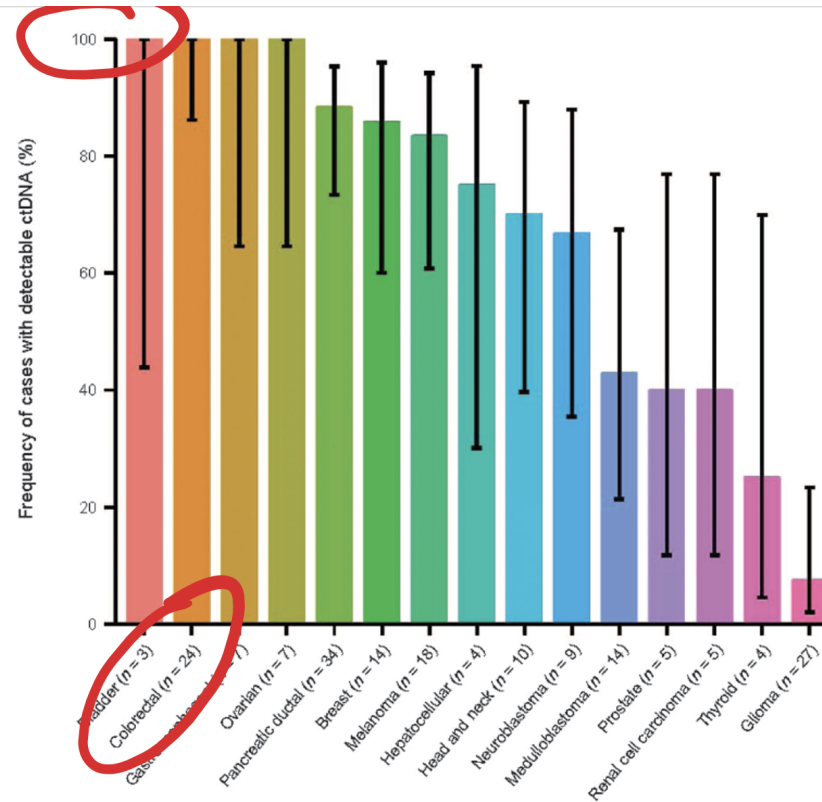
a



5

Why is colorectal a posterchild for liquid biopsies?

- Cannot forget biology; high-shedders versus low shedders.



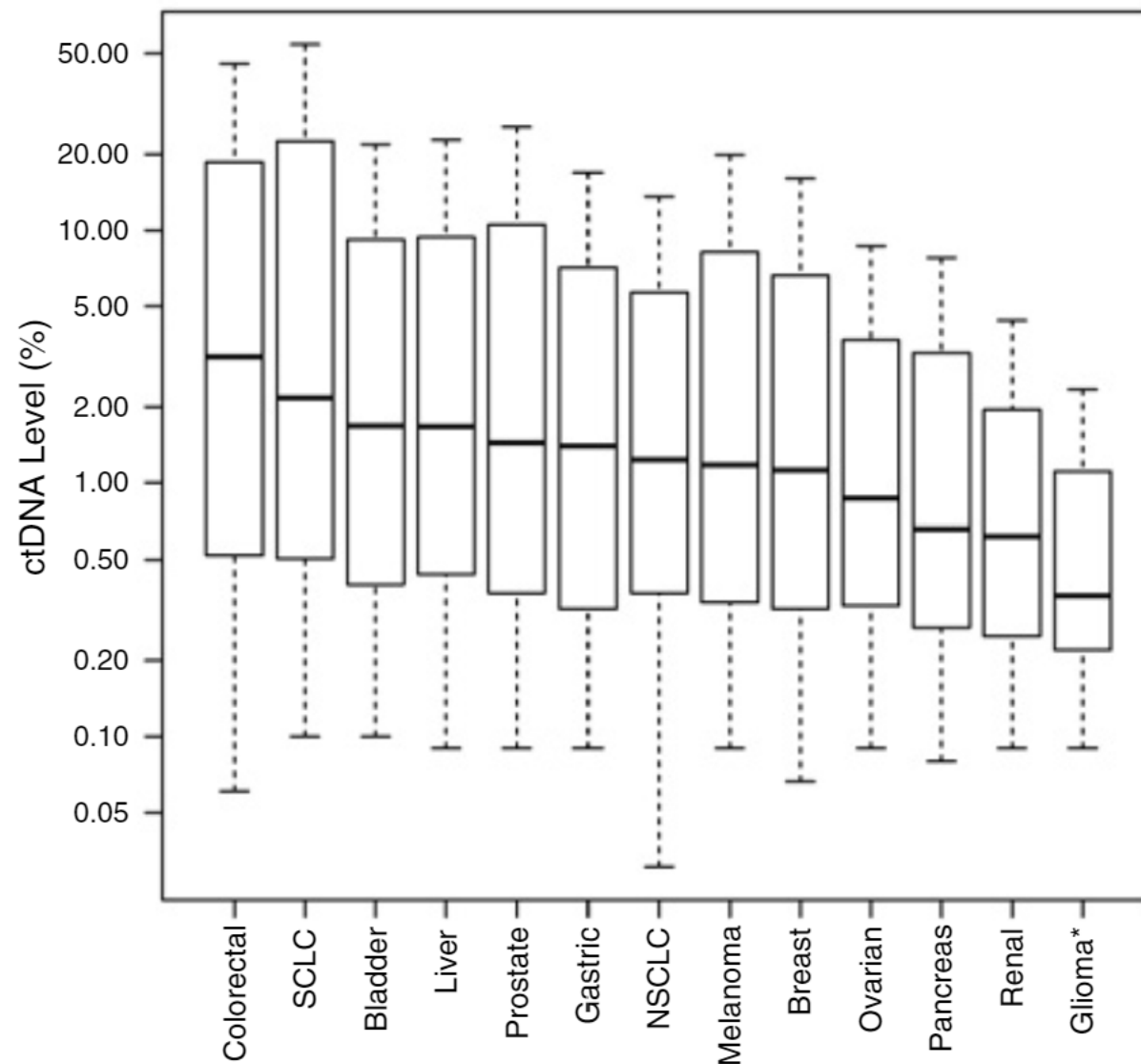
The Landscape of Actionable Genomic Alterations in Cell-Free Circulating Tumor DNA from 21,807 Advanced Cancer Patients



Oliver A. Zill¹, Kimberly C. Banks¹, Stephen R. Fairclough¹, Stefanie A. Mortimer¹,
James V. Vowles¹, Reza Mokhtari¹, David R. Gandara², Philip C. Mack², Justin I. Odegaard¹,
Rebecca J. Nagy¹, Arthur M. Baca¹, Helmy Eltoukhy¹, Darya I. Chudova¹, Richard B. Lanman¹,
and AmirAli Talasz¹

Clinical Cancer Research

August 2018
Volume 24, Issue 15



5

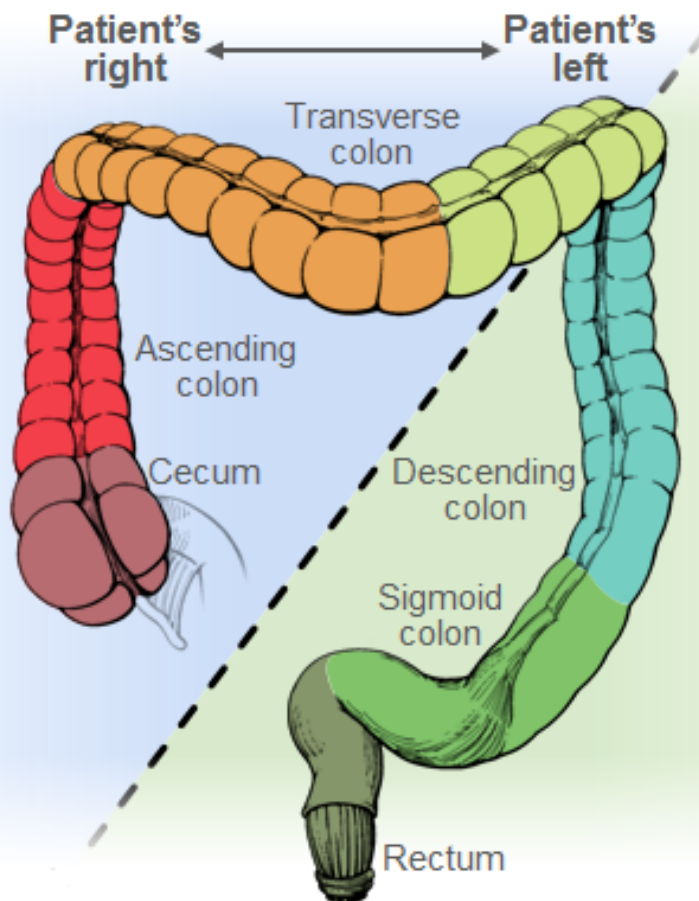
RIGHT vs. LEFT

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

5

Right-Sided
(N = 83)

93%

Left-Sided
(N = 334)

90%

Transverse
(N = 17)

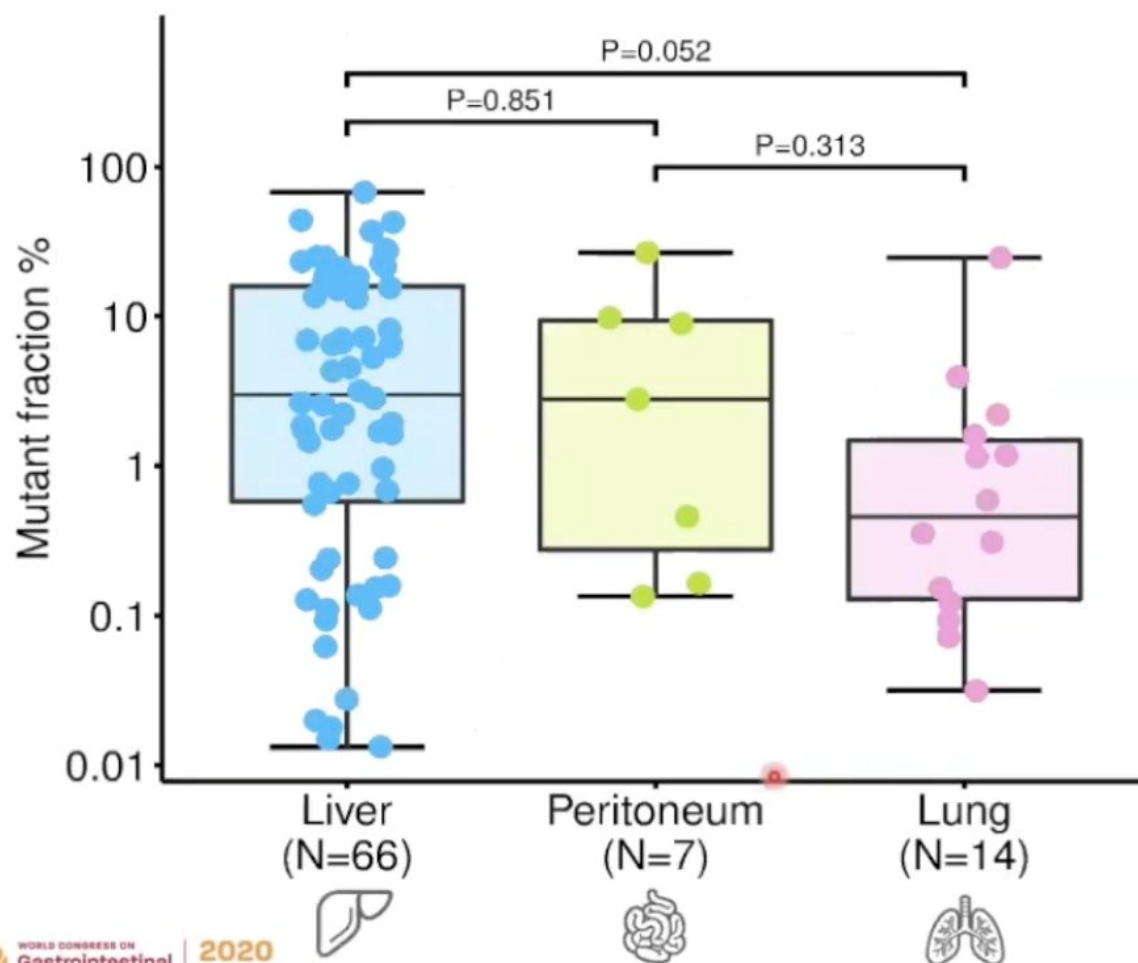
82%

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

DNA 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

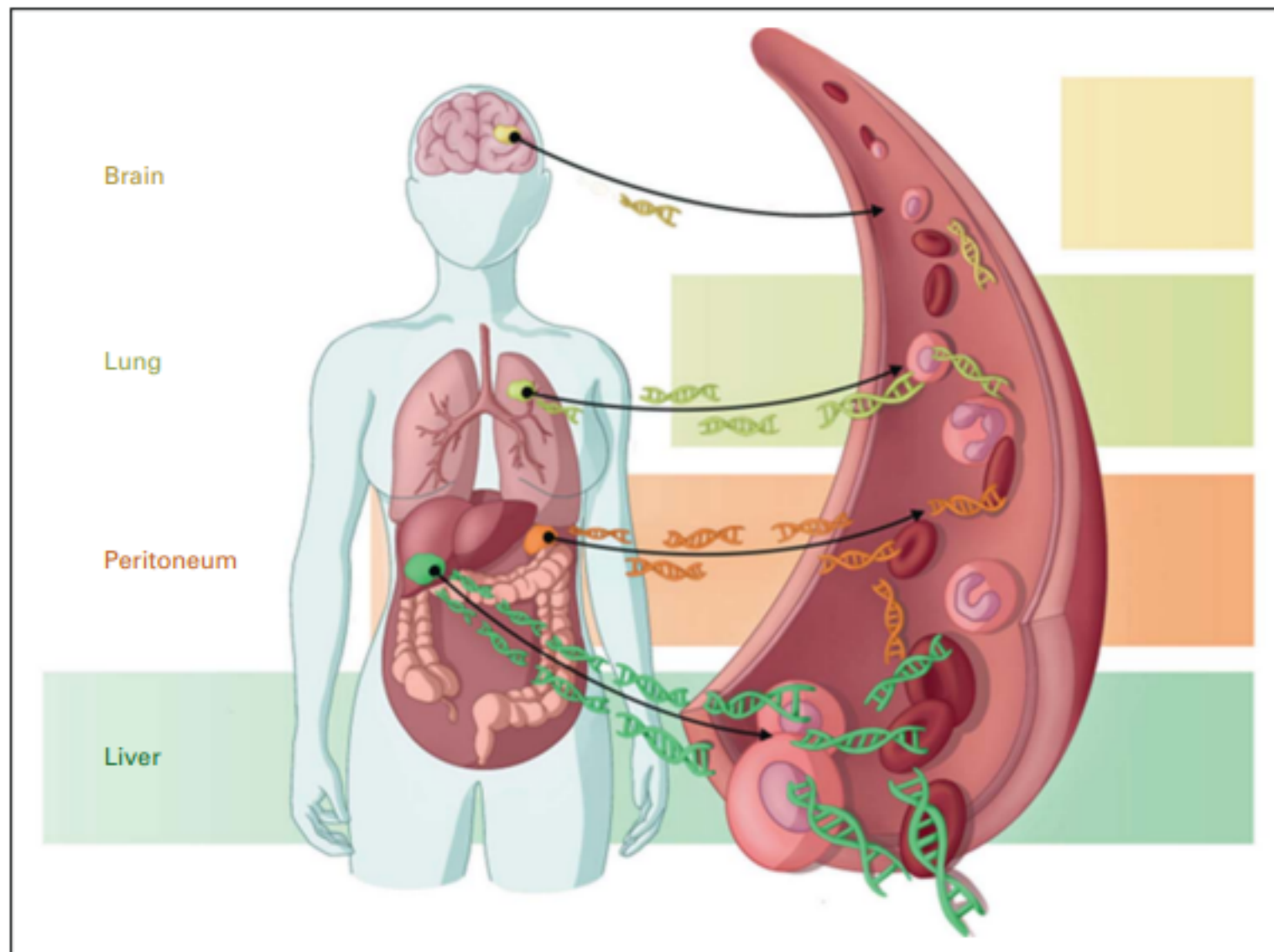


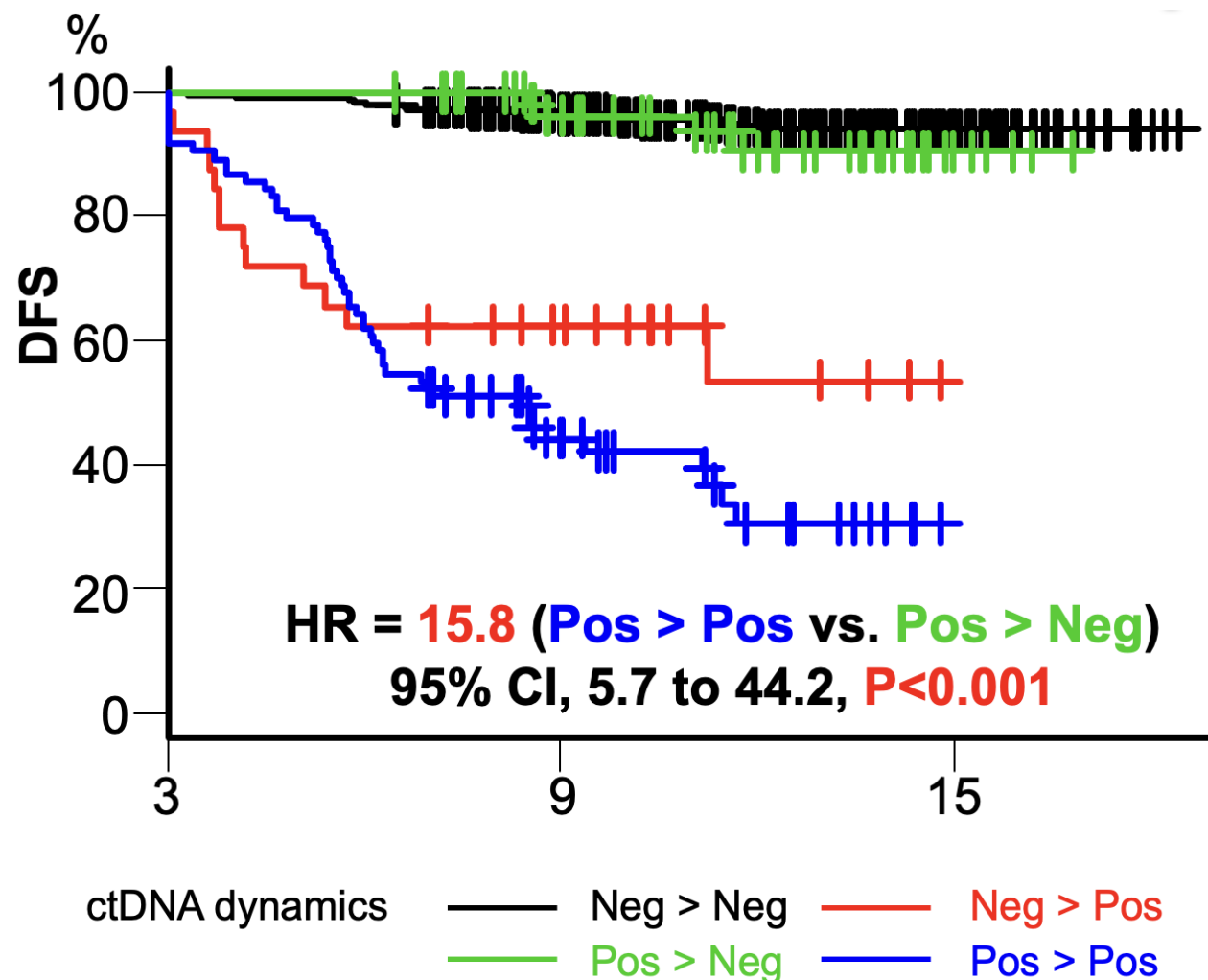
FIG 1. Shedding and amount of detectable circulating tumor DNA varies by location of metastatic site. Liver metastases appear to shed the most DNA, followed by the peritoneum and lung.



6

Beyond prognostic; is it predictive?

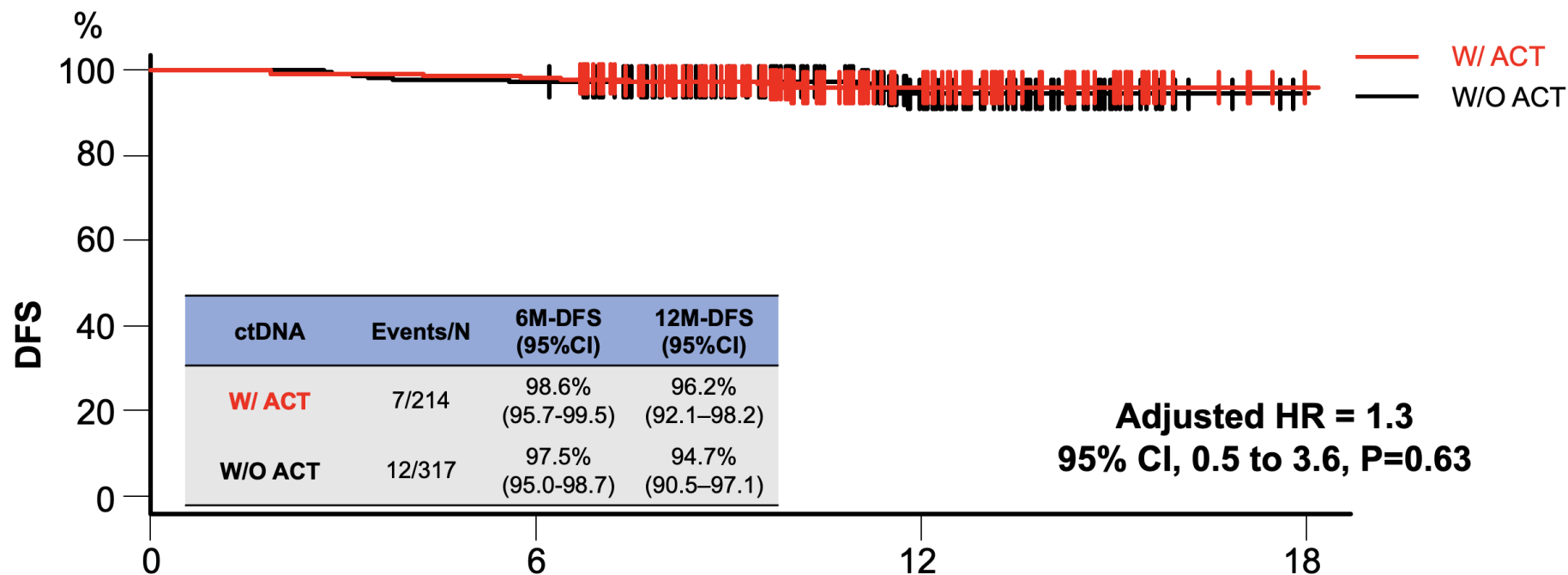
- Opening up clinical trial opportunities for both escalation and de-escalation.
- CIRCULATE-US



6

Beyond prognostic; is it predictive?

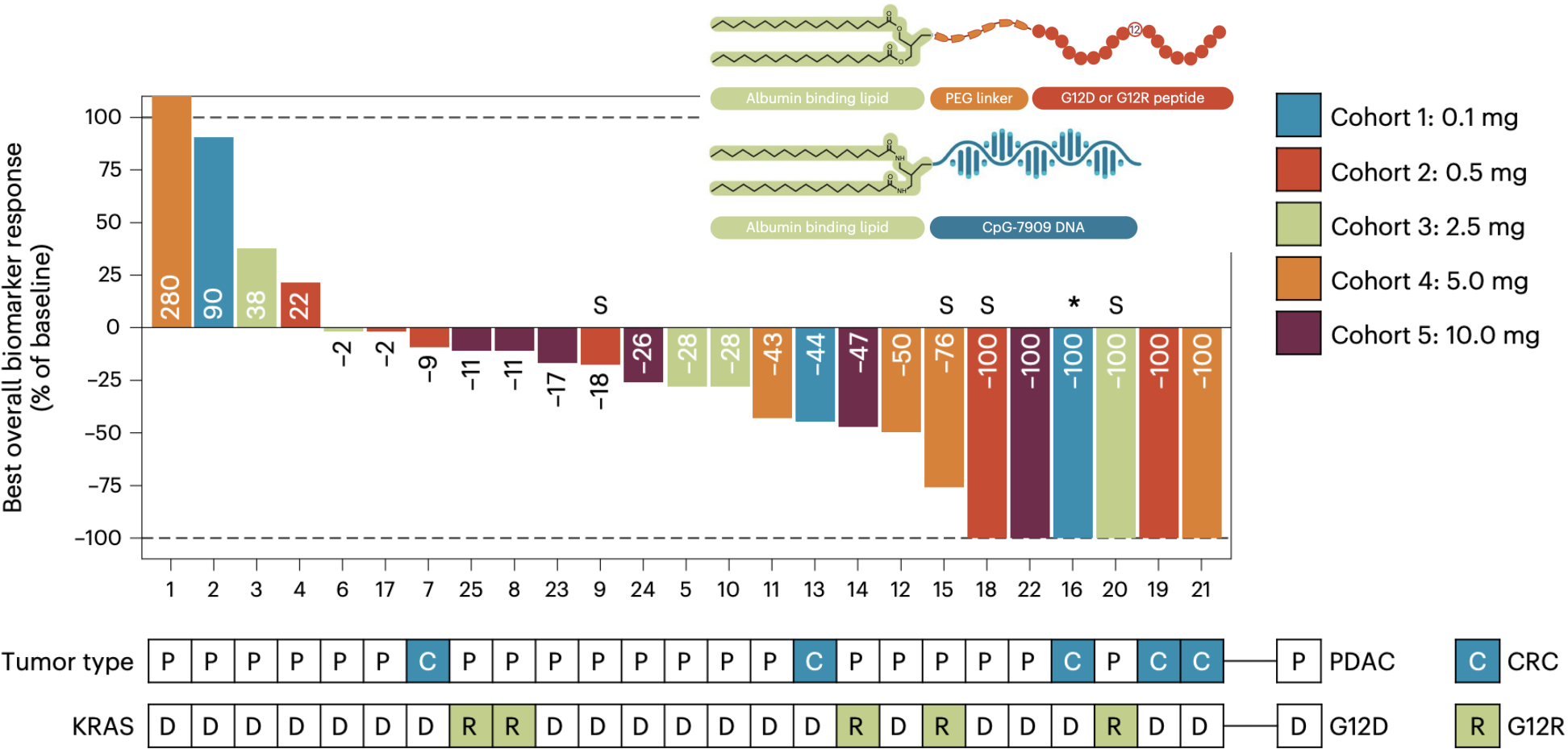
- Opening up clinical trial opportunities for both escalation and de-escalation.
- CIRCULATE-US



7

Innovative clinical trial designs

- Pairing with novel therapeutics



7

Surgery

Molecular Recurrence

ctDNA detectable at varying limits
based on shedding and organs involved

Clinical / Radiographic Recurrence

Micrometastases in various organs (eg, lung
present, but not initially detectable on scans)

Adjuvant Therapy

9 - 12 months

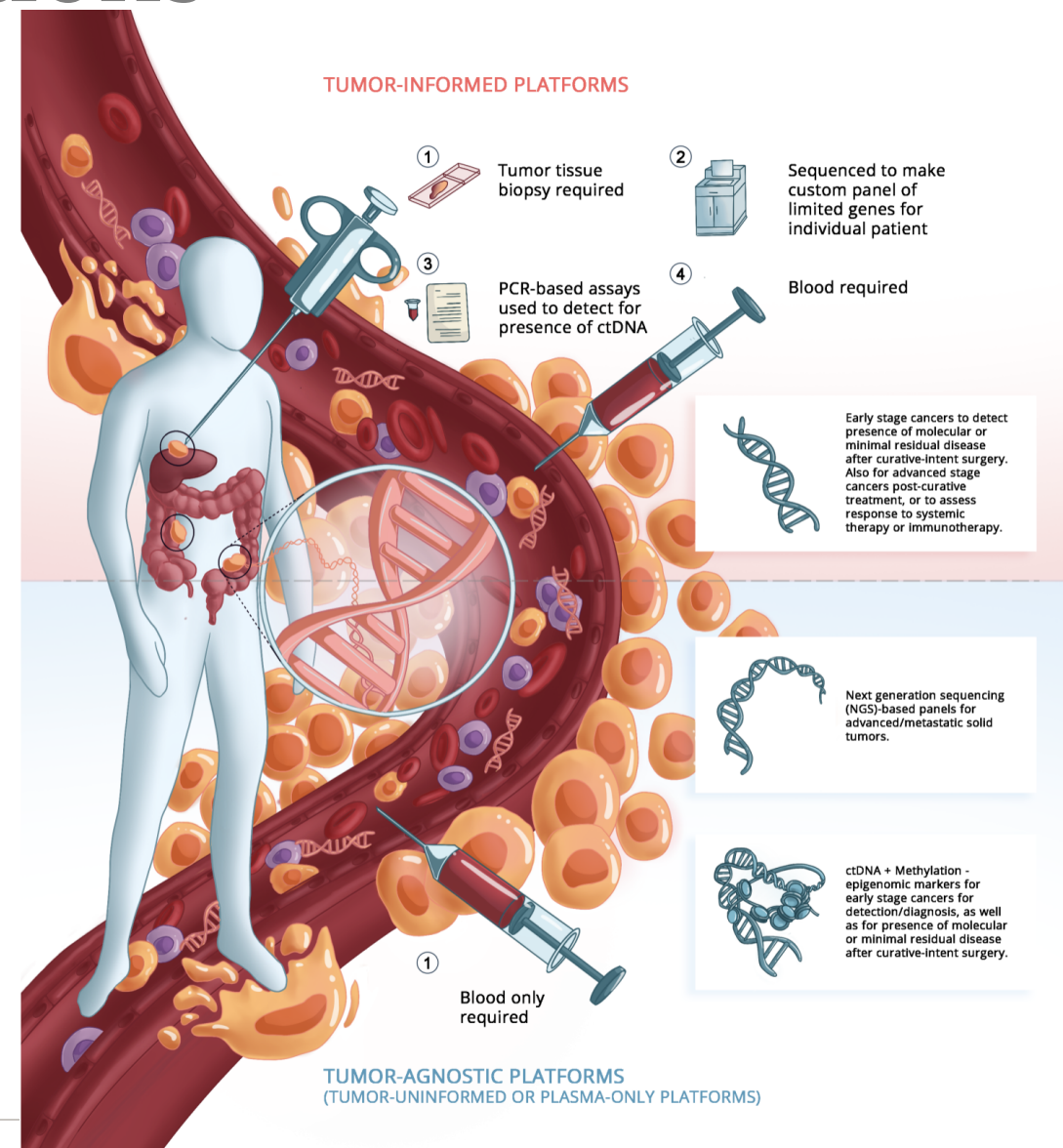
“Adjuvant-plus”

ASCO Daily News[®]

8

Multiple assay options

- Pros and Cons
- Plasma-only versus tumor-informed
- Whole-exome versus whole genome based assays



ASCO Daily News®

9

Ability to quantify and measure

- Improving sensitivity of current assays
- Different lenses looking at cancer

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

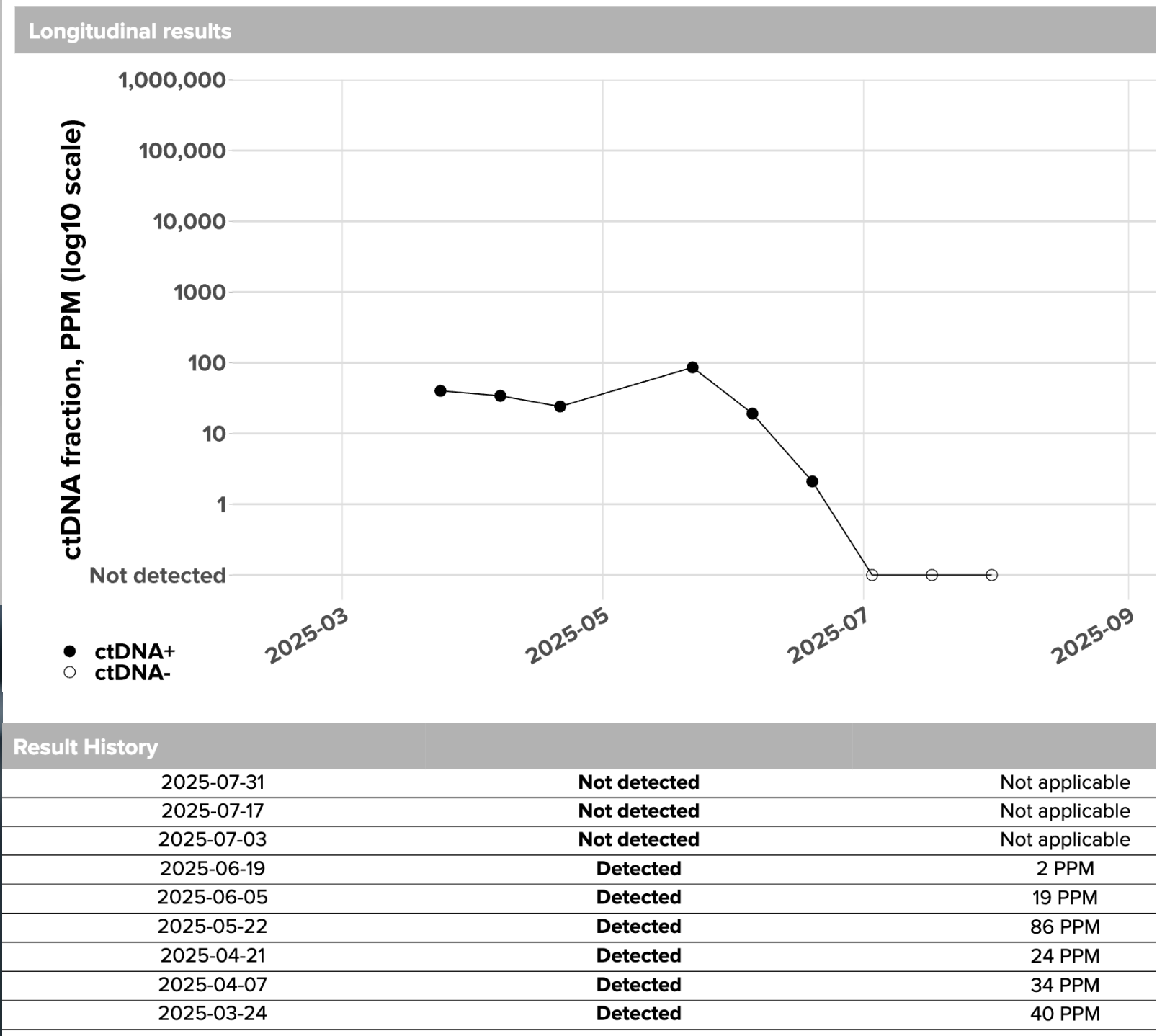
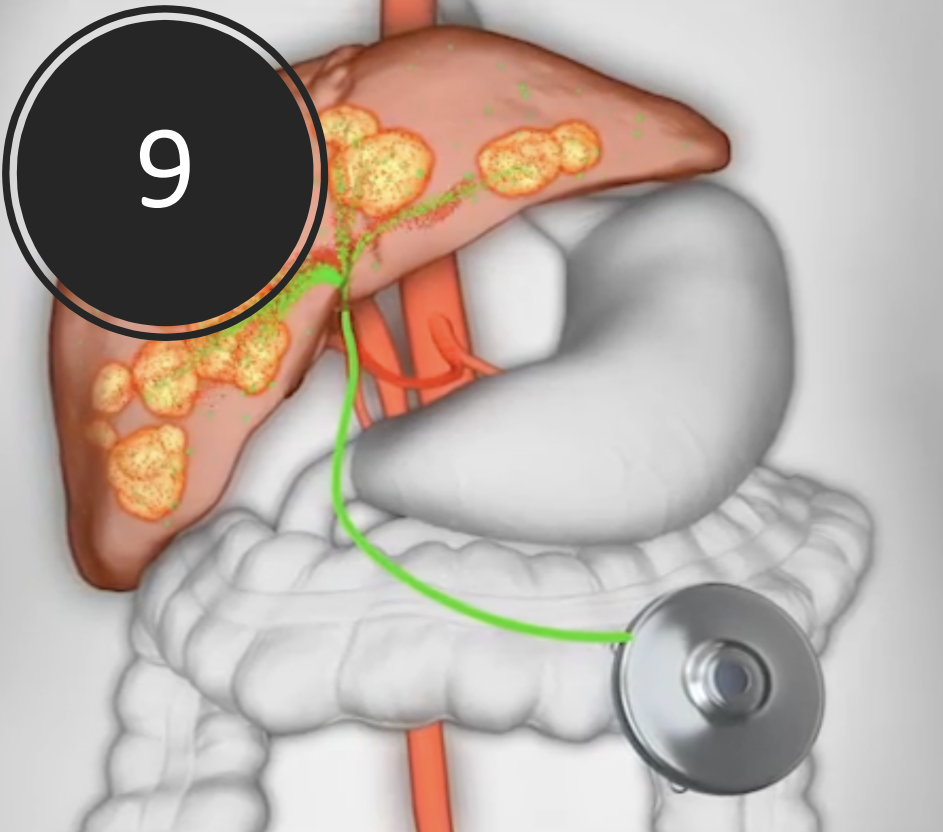
PPM

- Parts per million

Relative measurement

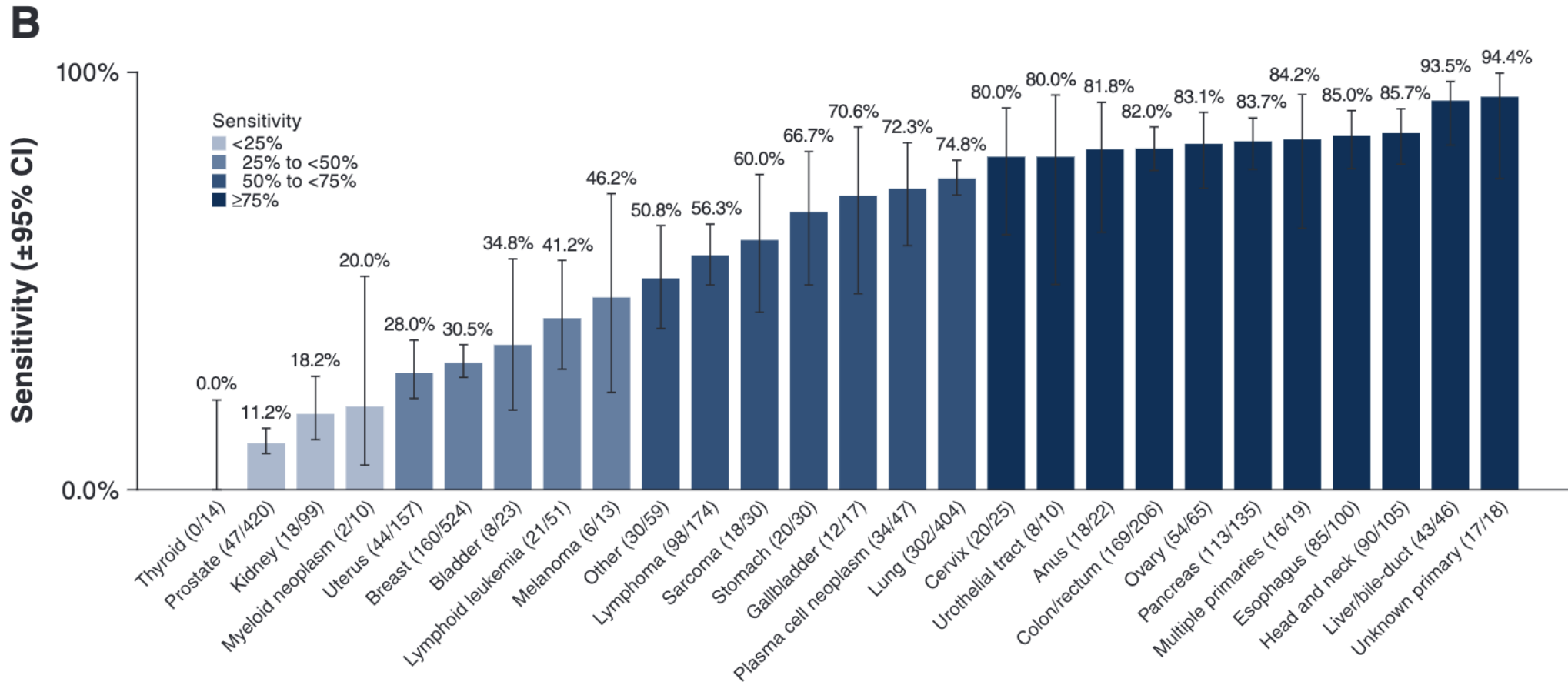
Focuses on the ratio of ctDNA molecules containing MRD targets out of the total cfDNA molecules measured (ctDNA + normal cfDNA)

$$1.67 \text{ parts per million (PPM)} = 1.67 \times 10^{-6} \text{ tumor fraction} \\ = 0.000167\% \text{ VAF}$$



Screening and Early Detection

- Colorectal Cancer specific tests
- Multi-Cancer Early Detection (MCED) assays



Screening and Early Detection

- Colorectal Cancer specific tests
- Multi-Cancer Early Detection (MCED) assays

Right-Sided
(N = 83)



Left-Sided
(N = 334)

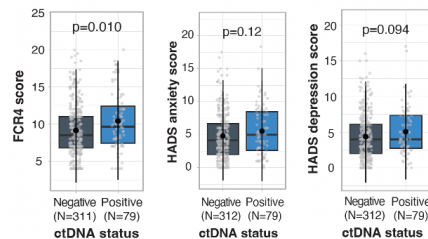


Transverse
(N = 17)

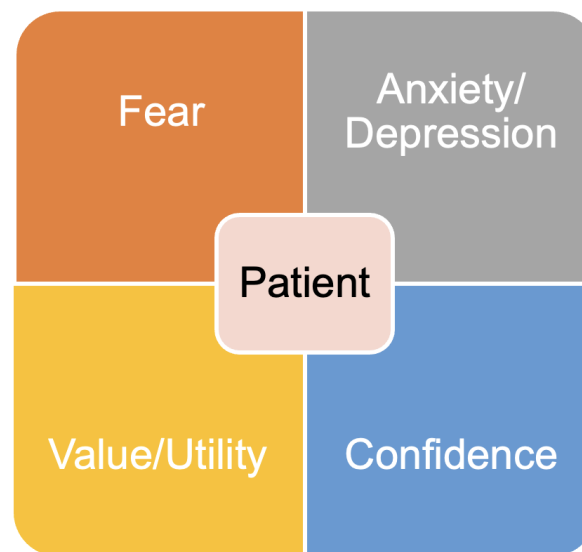
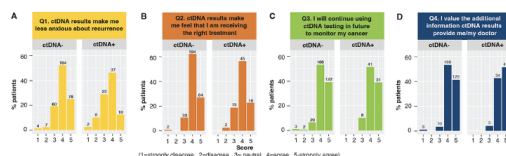


- Perceived utility

Perceived utility of ctDNA testing and dimensions of well-being



**~1130 responses from
413 patients**



73%

reported ctDNA results
reduced anxiety about
cancer recurrence

87%

felt they were receiving
the right treatment after
receiving their results

92%

would continue using
the ctDNA test to
monitor cancer

96%

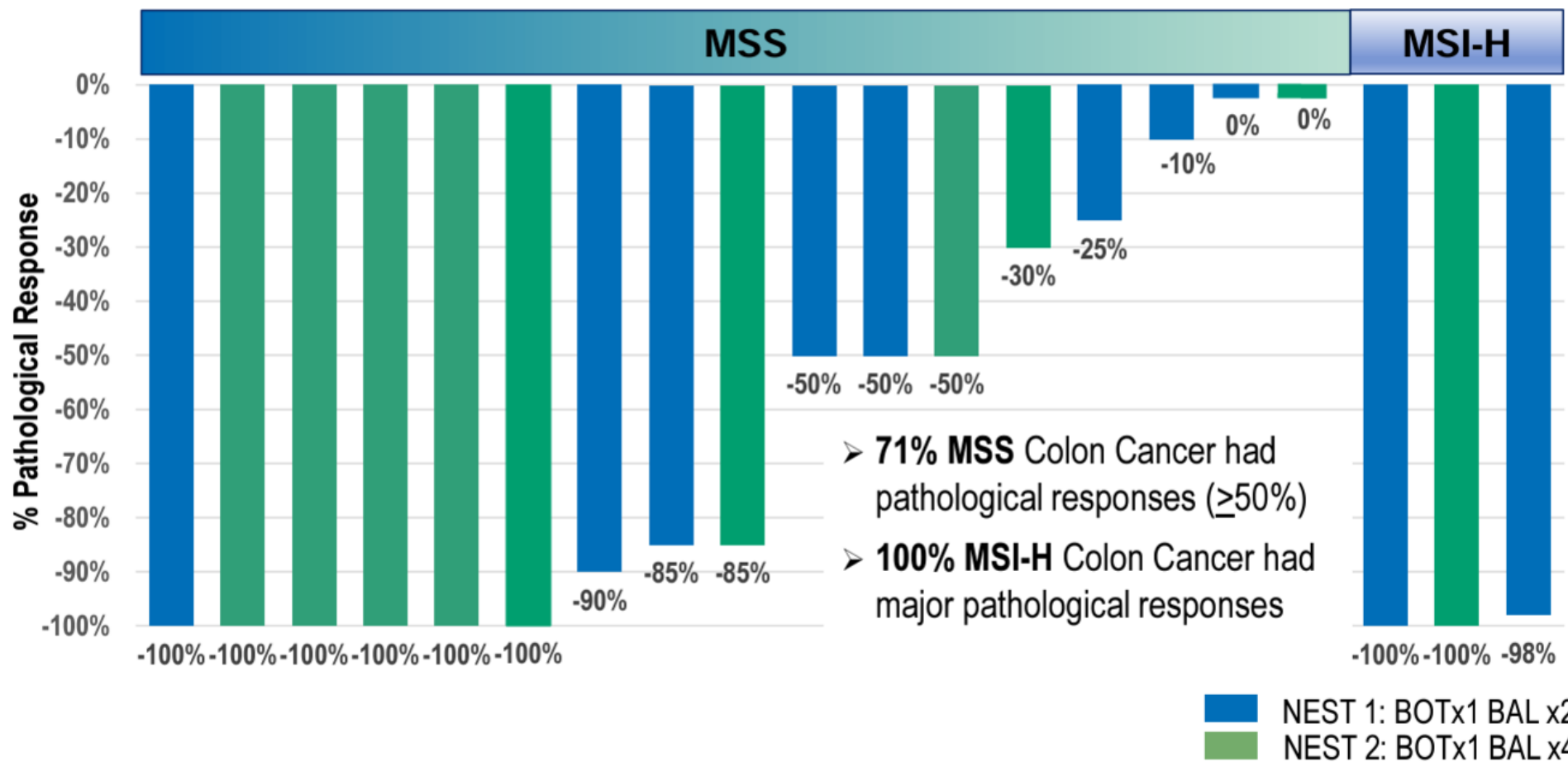
valued the additional
information received
from ctDNA results

Kasi PM, et al. Poster Session C, Abstract ID: 54

Neoadjuvant paradigm shift

- Organ Preservation and increasing the proportion of patients who can be cured.

PATHOLOGICAL TUMOR REDUCTIONS (%) BY PATIENT

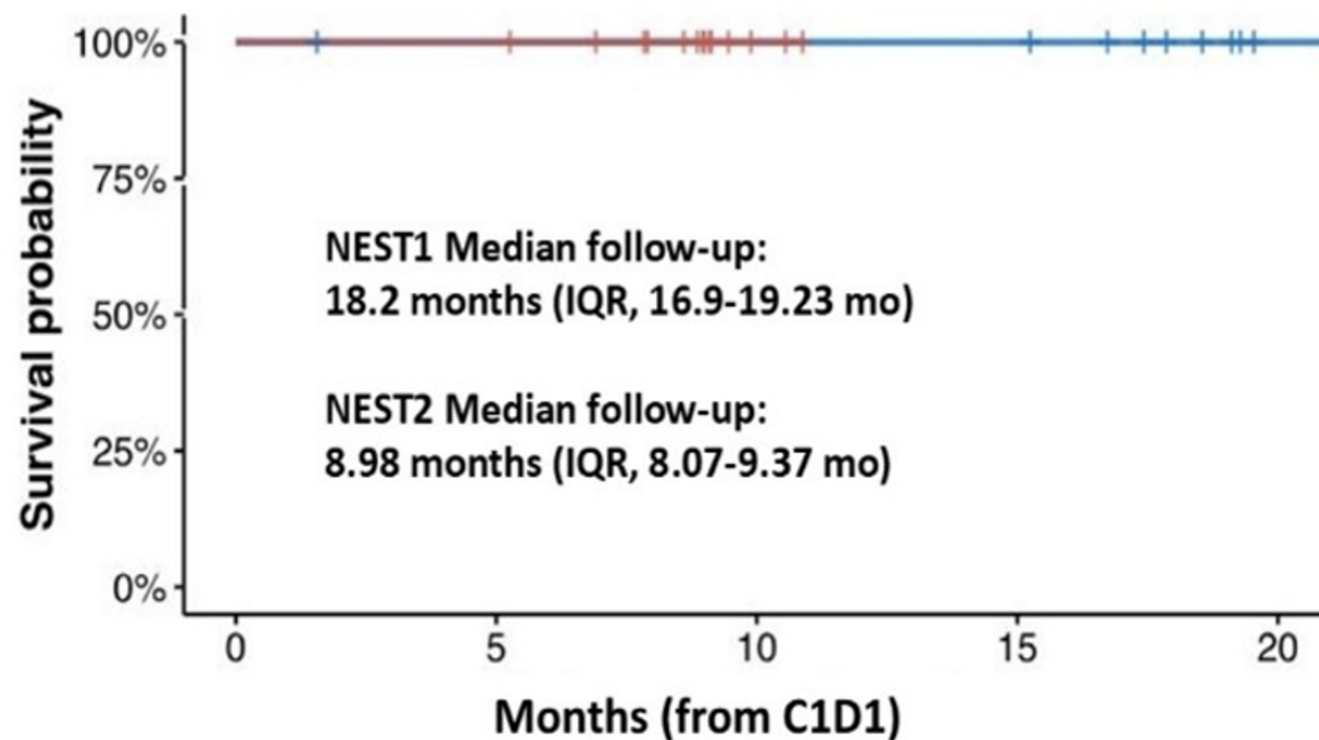


- Organ Preservation and increasing the proportion of patients who can be cured.

NEST 1/2 PFS

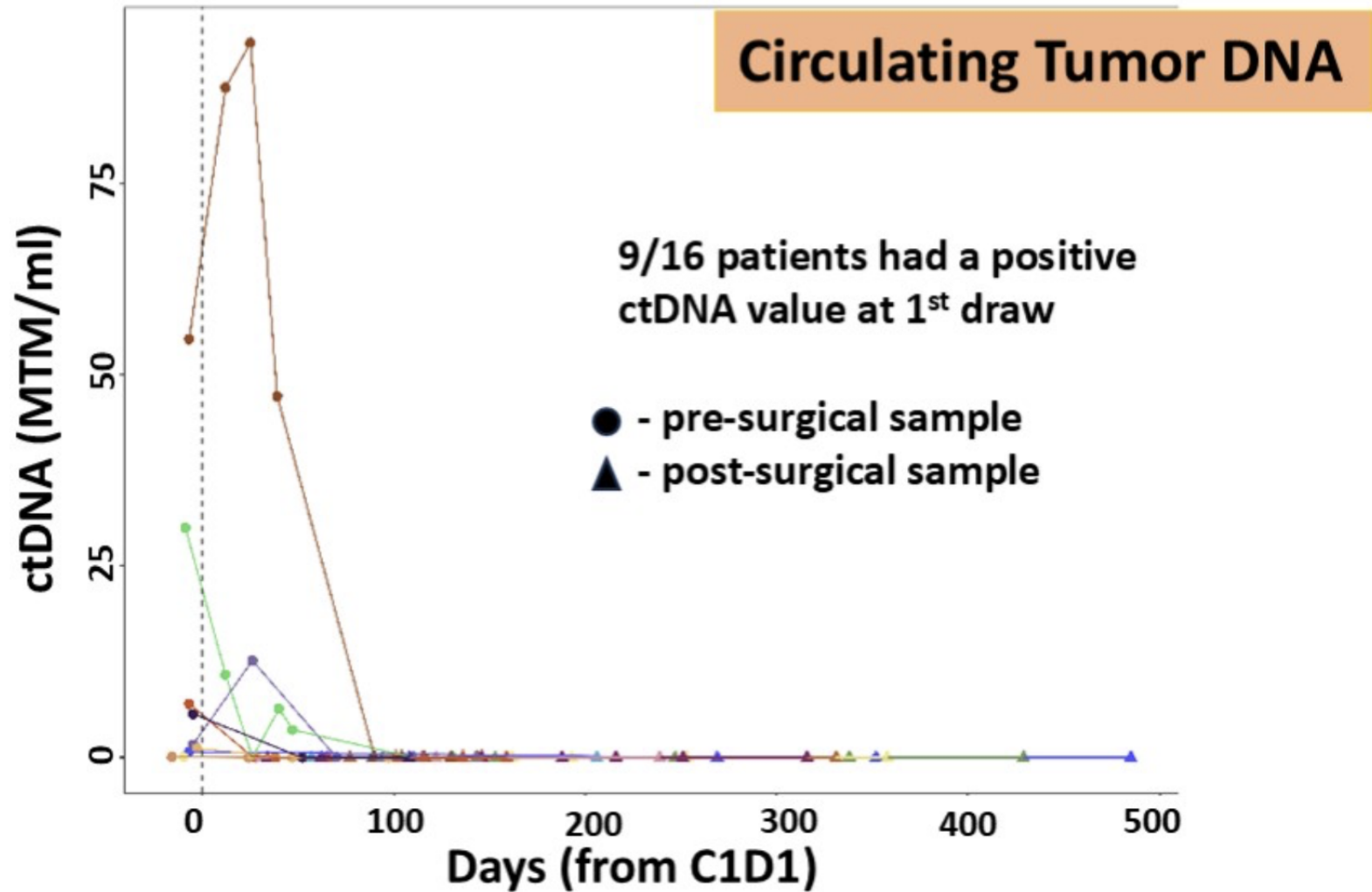
Progression Free Survival

NEST1 NEST2



12) Neoadjuvant paradigm shift

- Organ Preservation and increasing the proportion of patients who can be cured.

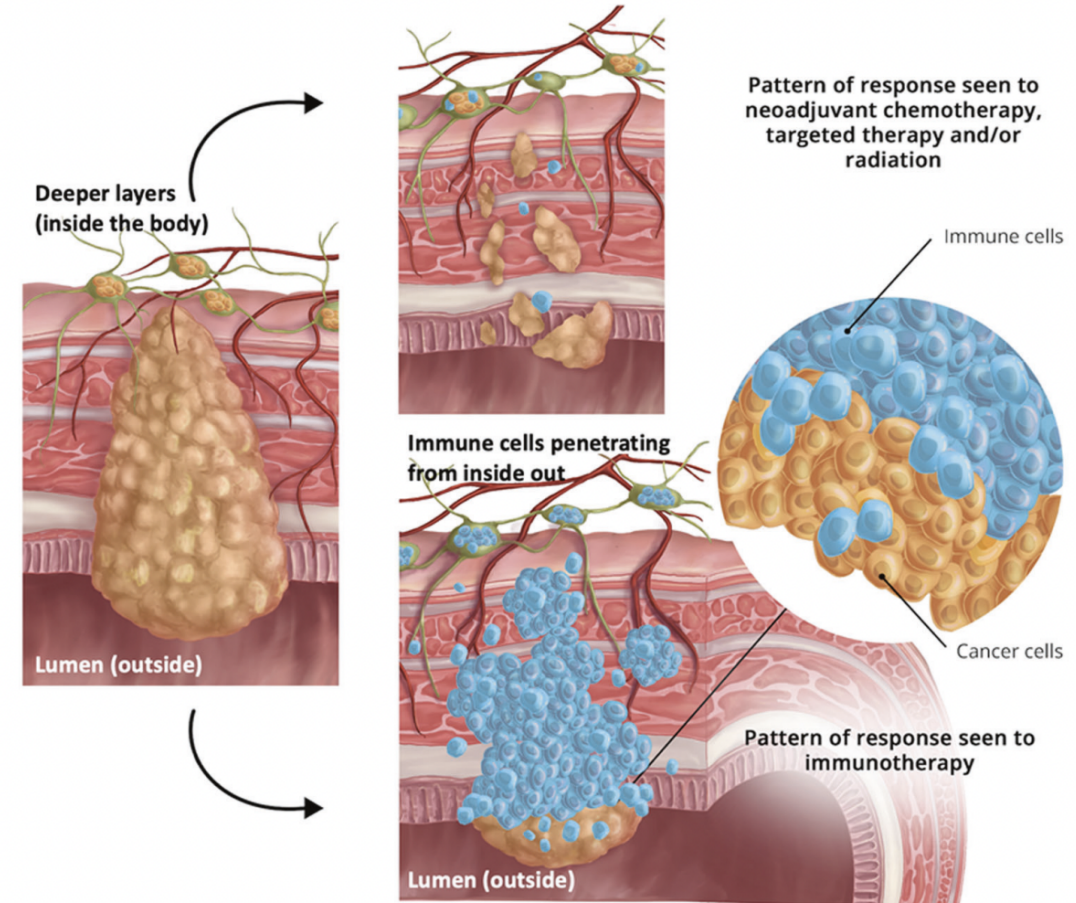


ARTICLE OPEN

Neoadjuvant botensilimab plus balstilimab response pattern in locally advanced mismatch repair proficient colorectal cancer

Pashtoon Murtaza Kasi¹✉, Manuel Hidalgo¹, Mehraheh D. Jafari², Heather Yeo^{2,3}, Lea Lowenfeld², Uqba Khan¹, Alana T. H. Nguyen¹, Despina Siolas¹, Brandon Swed¹, Jini Hyun¹, Sahrish Khan¹, Madeleine Wood¹, Benjamin Samstein², Juan P. Rocca², Allyson J. Ocean¹, Elizabeta C. Popa¹, Daniel H. Hunt², Nikhil P. Uppal¹, Kelly A. Garrett², Alessio Pigazzi², Xi Kathy Zhou^{1,3}, Manish A. Shah¹ and Erika Hissong⁴

Check for updates



Forbes

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EDITORS' PICK

New Drug Combo Shows Promising Results Against Early Stages Of Colorectal Cancer



Pathologist Erika Hissong (L) and Oncologist Pashtoon Kasi (R) were two of the scientists involved in a new study demonstrating efficacy of a new immunotherapy against colorectal cancer. WEILL-CORNELL MEDICINE

A combination immunotherapy developed by biotech company Agenus administered before surgery destroyed over 80% of a tumor before it was removed.



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An American Society of Clinical Oncology Journal

SPECIAL SERIES: PRECISION MEDICINE AND IMMUNOTHERAPY IN GI MALIGNANCIES

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

Midhun Malla, MD, MS¹; Jonathan M. Loree, MD, MS²; Pashtoon Murtaza Kasi, MD, MS³; and Aparna Raj Parikh, MD⁴

THE LANCET

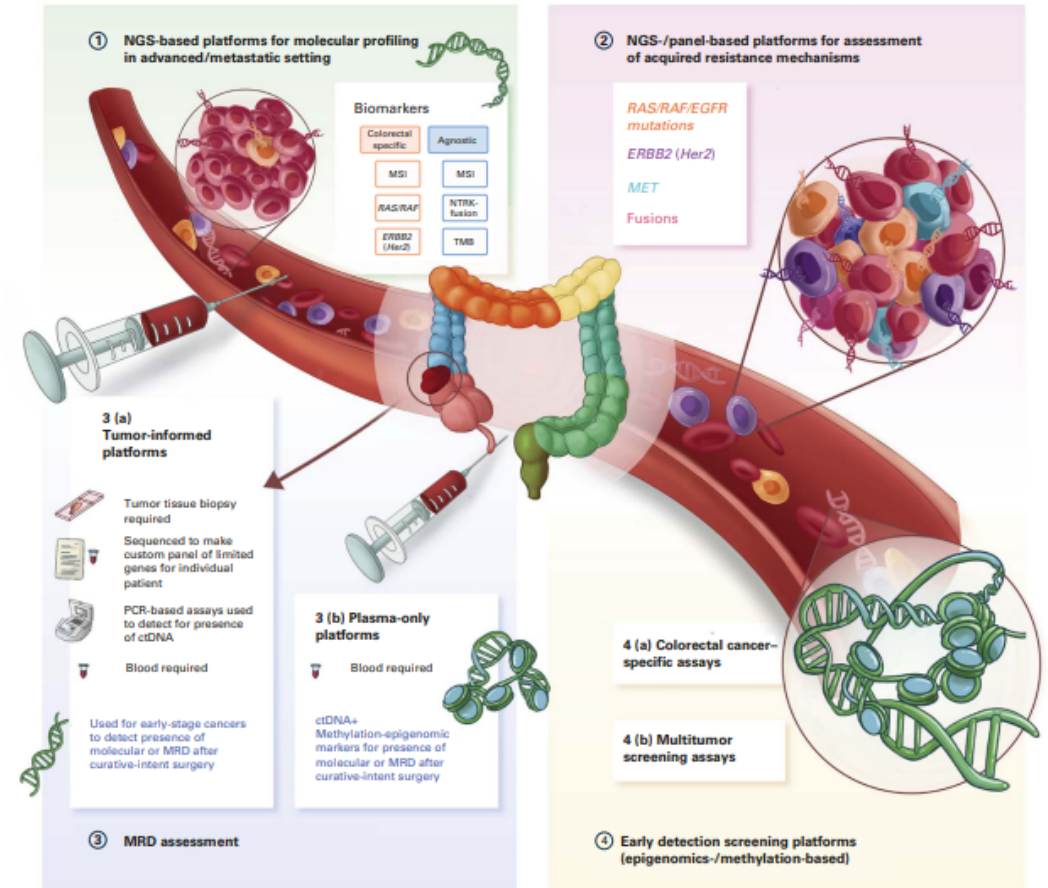
doi: 10.1016/S0140-6736(19)32319-0.

PMID: 31631858.

Colorectal cancer

Evelien Dekker, Pieter J Tanis, Jasper L A Vleugels, Pashtoon M Kasi, Michael B Wallace

Liquid Biopsies (ctDNA) in Clinic for Colorectal Cancer





Multidisciplinary Approaches to Cancer Symposium

Debate: ctDNA Should Be Incorporated Into Active Management of Colorectal Cancer Patients ~ Focus: Pro argument

Pashtoon Murtaza Kasi, MD, MS

Endowed Rad Family Chair in Gastrointestinal Oncology

Medical Director GI Oncology, City of Hope Orange County

Associate Professor, Department of Medical Oncology & Therapeutics Research
City of Hope

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