City of Hope

ANNUAL

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

ctDNA's Role in Shaping the Present and Future of GI Cancer Treatment

Pashtoon Kasi, MD, MS

Medical Director of GI Oncology

Rad Family Chair in Gastrointestinal Oncology

City of Hope Orange County

kasi@coh.org

X: @pashtoonkasi

Disclosures

- Founder of Precision BioSciences

This disclosure has been deemed as irrelevant, as this presentation is limited to basic science research, such as pre-clinical research and drug discovery, or the methodologies of research, and I will not make care recommendations.

- 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
- Grant/Research for Agenus, Merck, Novartis; and Scientific Board Advisor for Elicio Therapeutics

The 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:

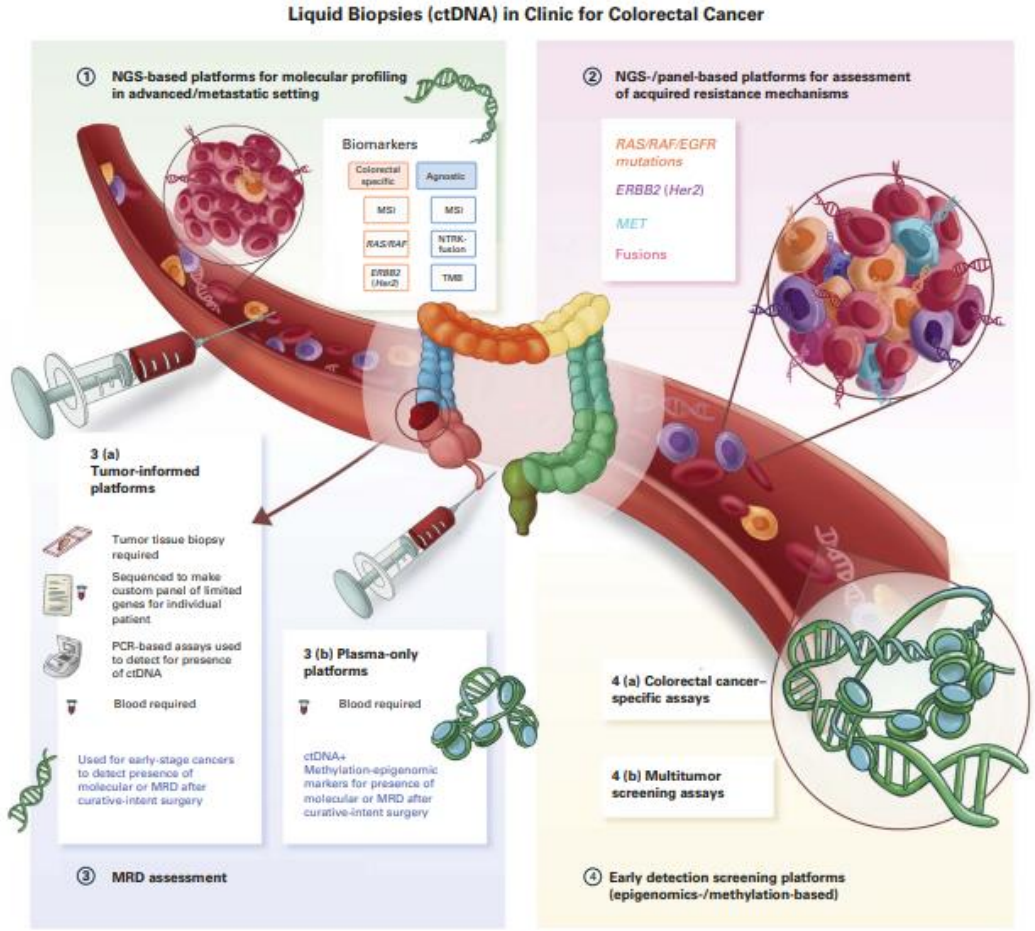
- Barriers to uptake of liquid biopsies into standard of care.
- Address disparities due to perceptions and treatment decisions relating to utility of liquid biopsies.

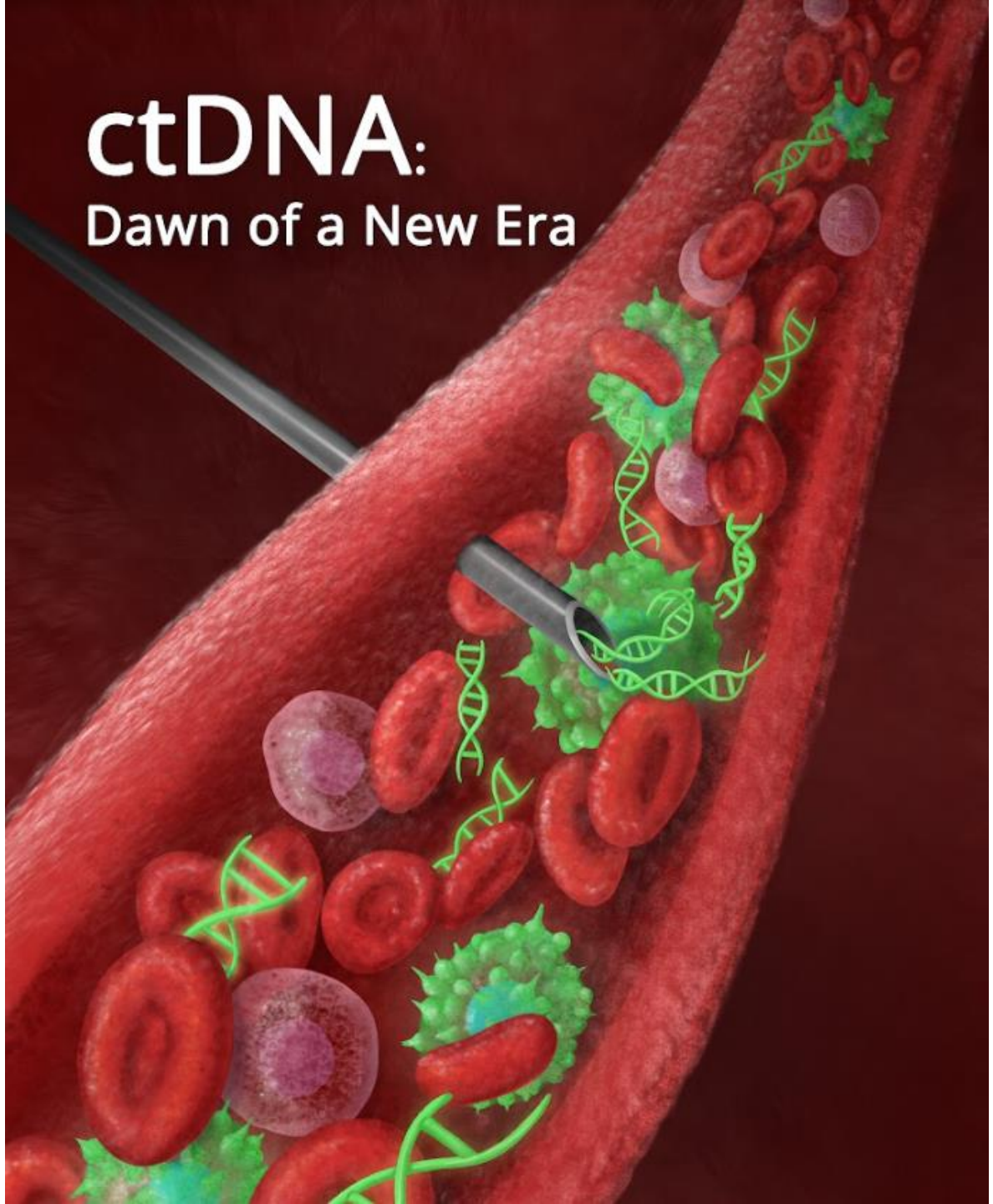
SPECIAL SERIES: PRECISION MEDICINE AND IMMUNOTHERAPY IN GI MALIGNANCIES

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



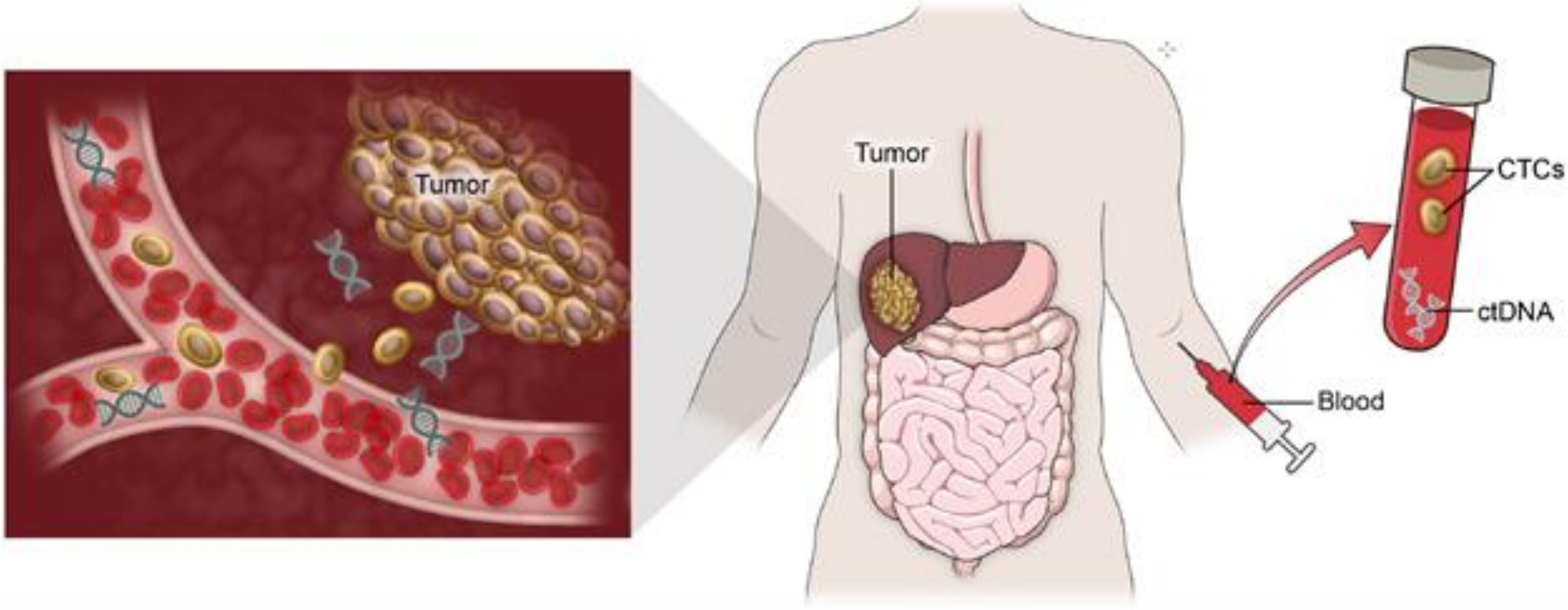


ctDNA: Dawn of a New Era

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

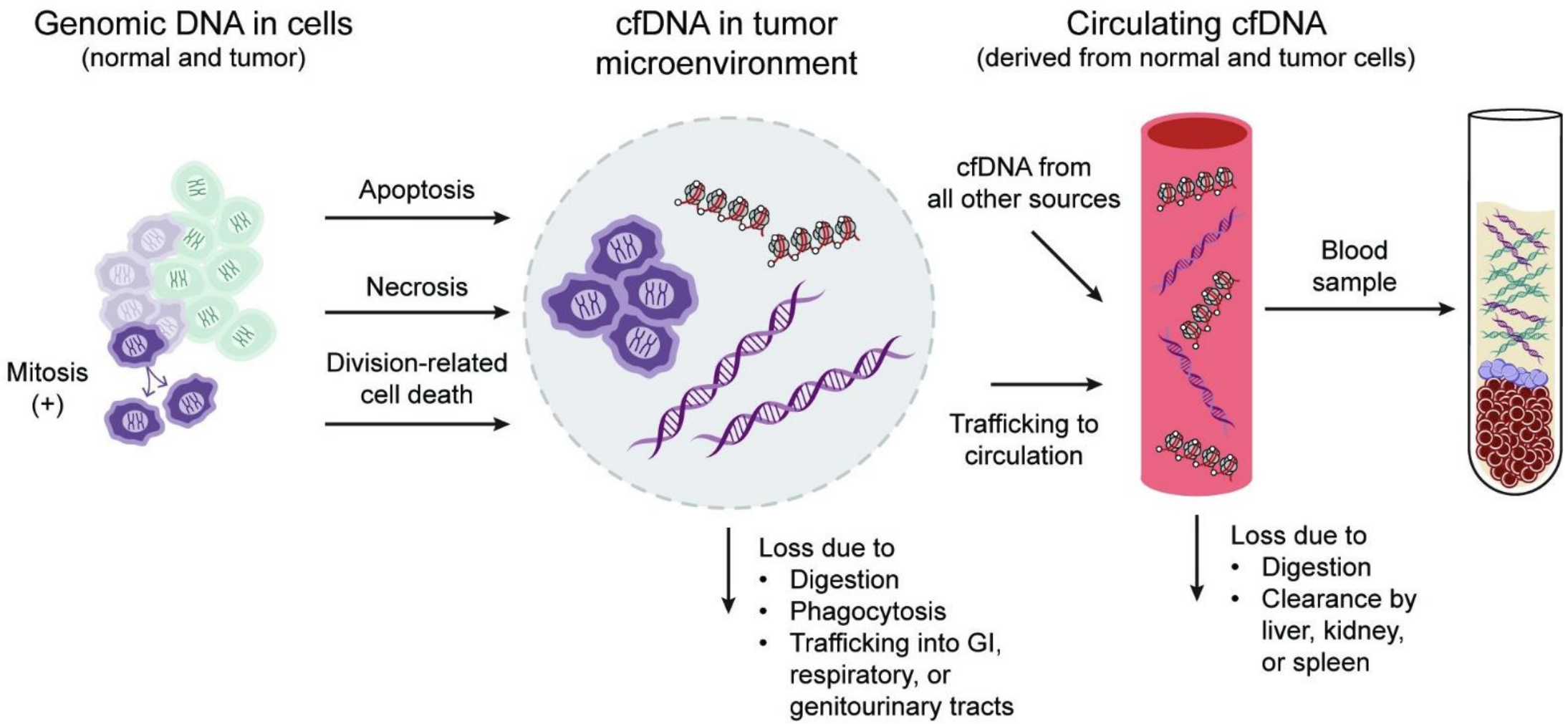
2022 ASCO® ANNUAL MEETING

ADVANCING EQUITABLE CANCER CARE THROUGH INNOVATION

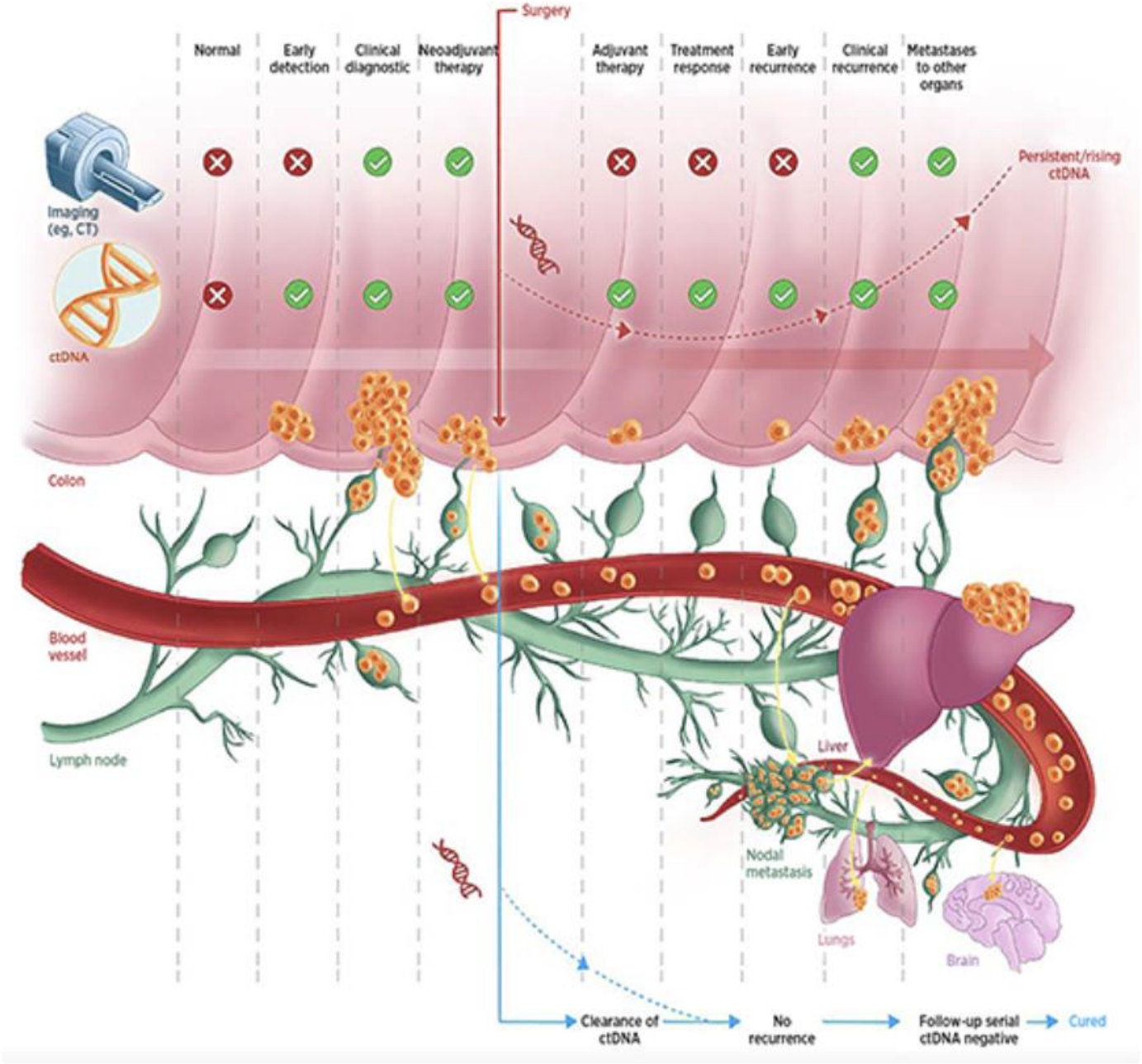


@pashtoonkasi

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



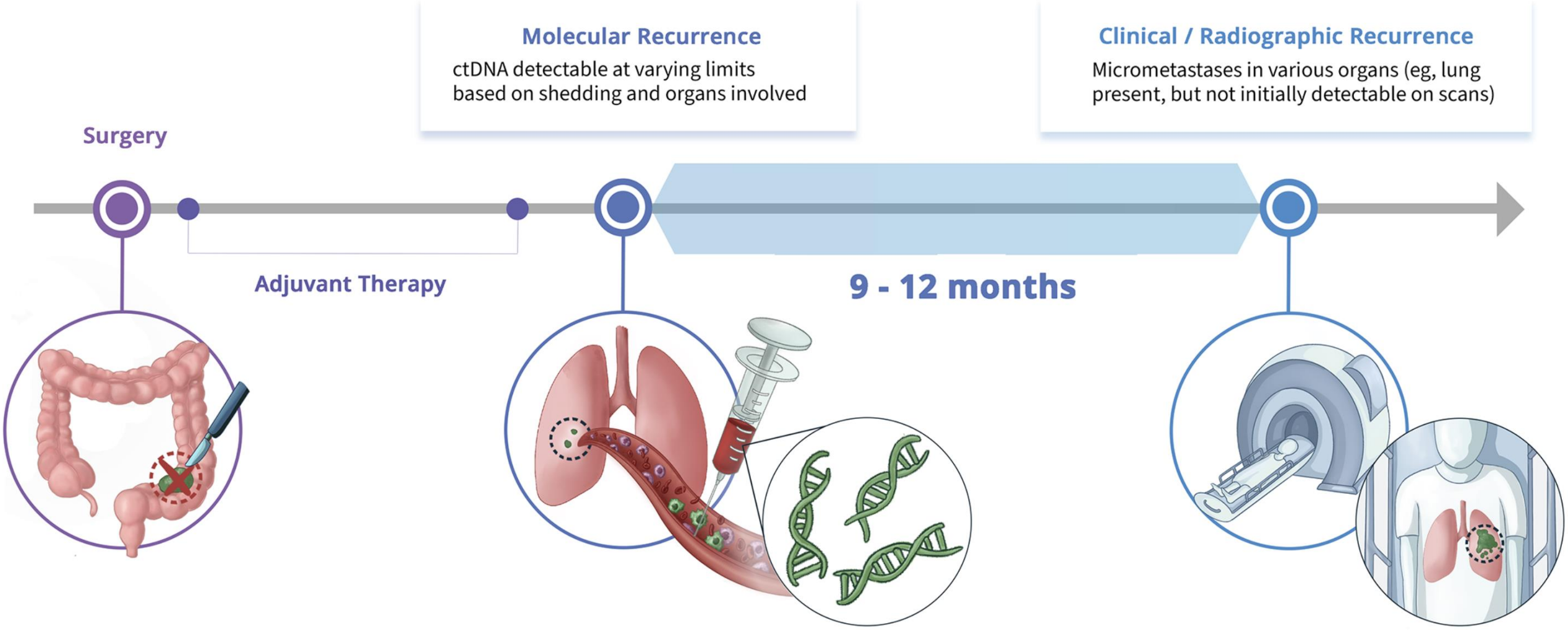
Bredno, J. et al, 2021. Clinical correlates of circulating cell-free DNA tumor fraction. PLOS ONE 16, e0256436.



- 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.

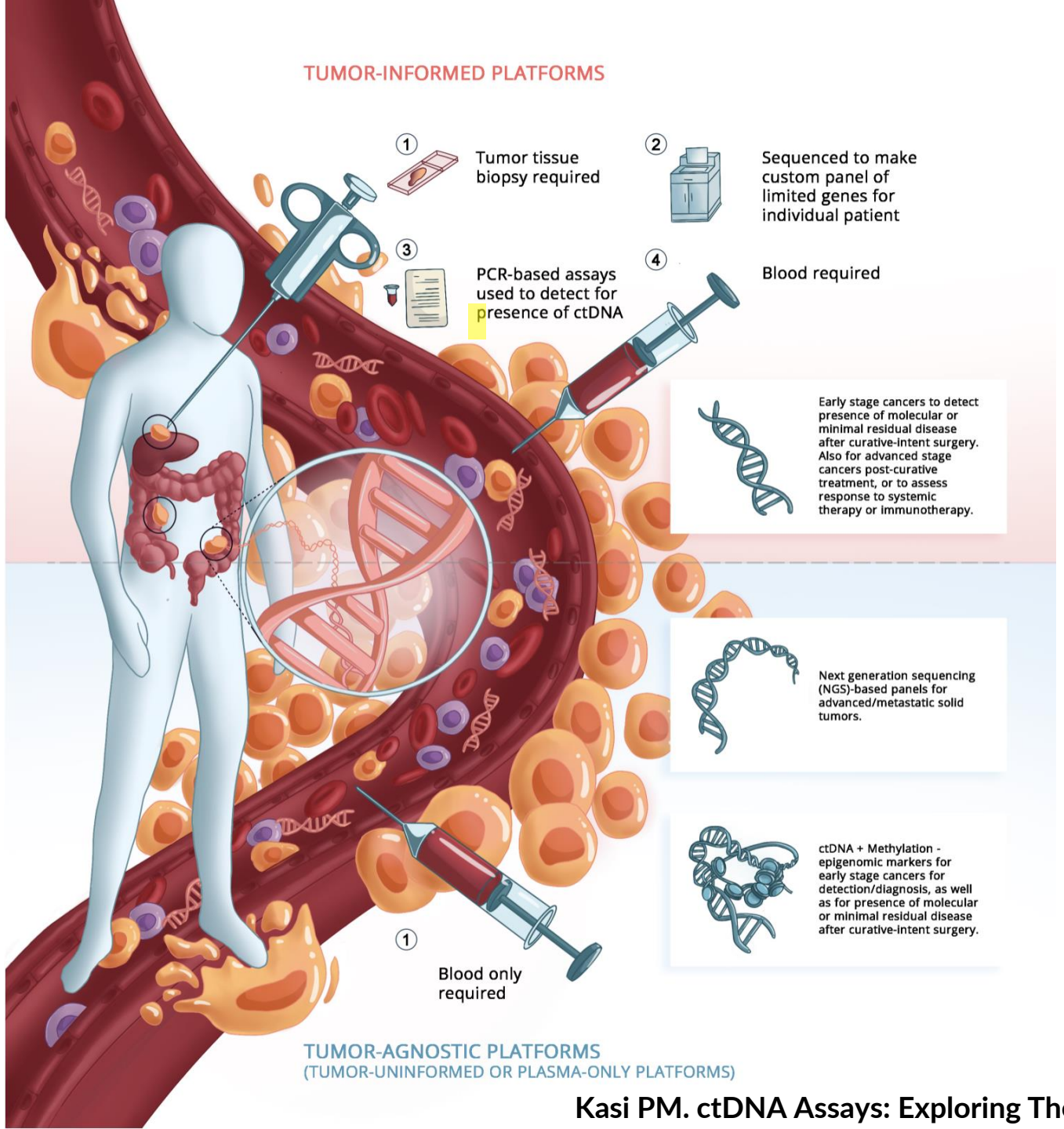


"Adjuvant-plus"

ASCO Daily News®

Kasi PM. Utility and Debate of Liquid Biopsy Assays in Surveillance Setting. March 2023. ASCO Daily News.

Settings/Platforms/Biology

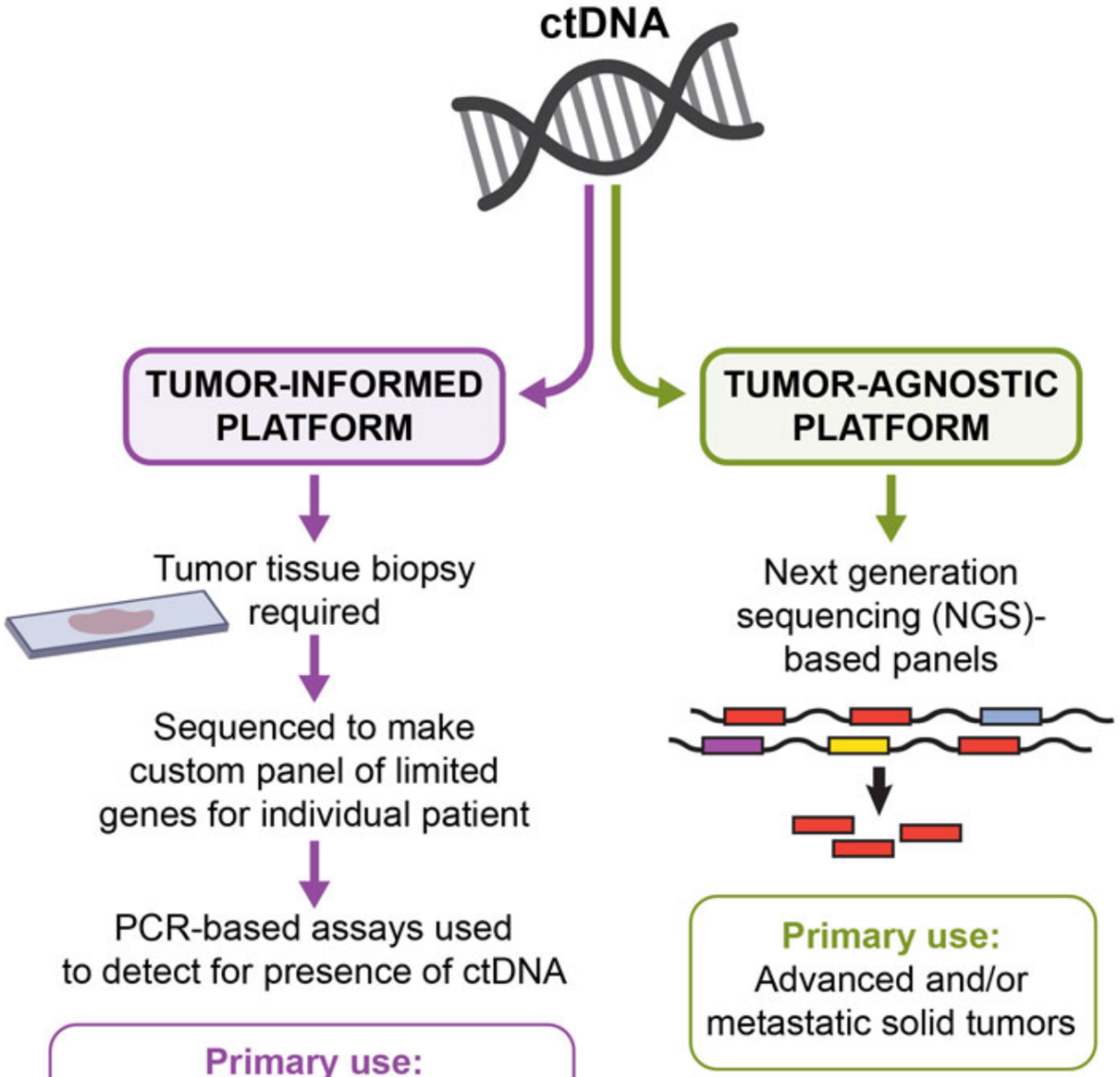


Tumor-informed Platforms Versus Tumor-agnostic (tumor-uninformed or plasma-only) Platforms

ASCO Daily News®

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

Figure 1. ctDNA Testing Platforms.



Tumor-informed

- Personalized for each patient's tumor
- Needs tumor tissue sent

Tumor-naïve

- ctDNA + Epigenetic signatures
- Methylation markers

ASCO Daily News®

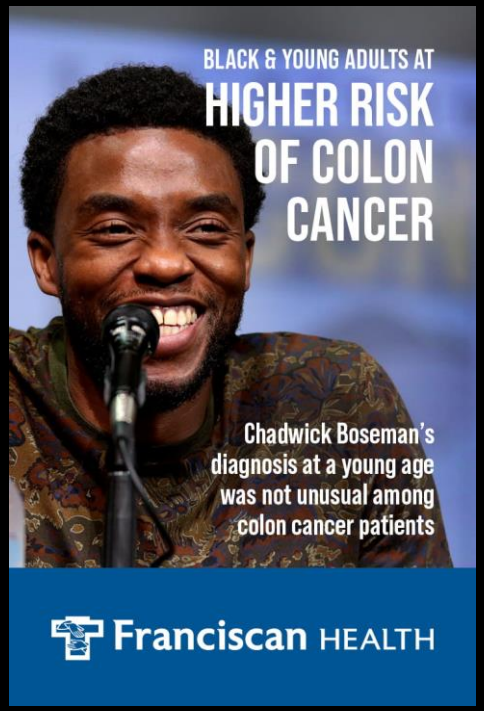
Kasi PM. ASCO Daily News. Kinetics of Liquid Biopsies in Predicting Response to Immunotherapy. Oct 1, 2020.

SECTIONS HOME SEARCH

The New York Times

WELL | LIVE

More Young People Are Dying of Colon Cancer



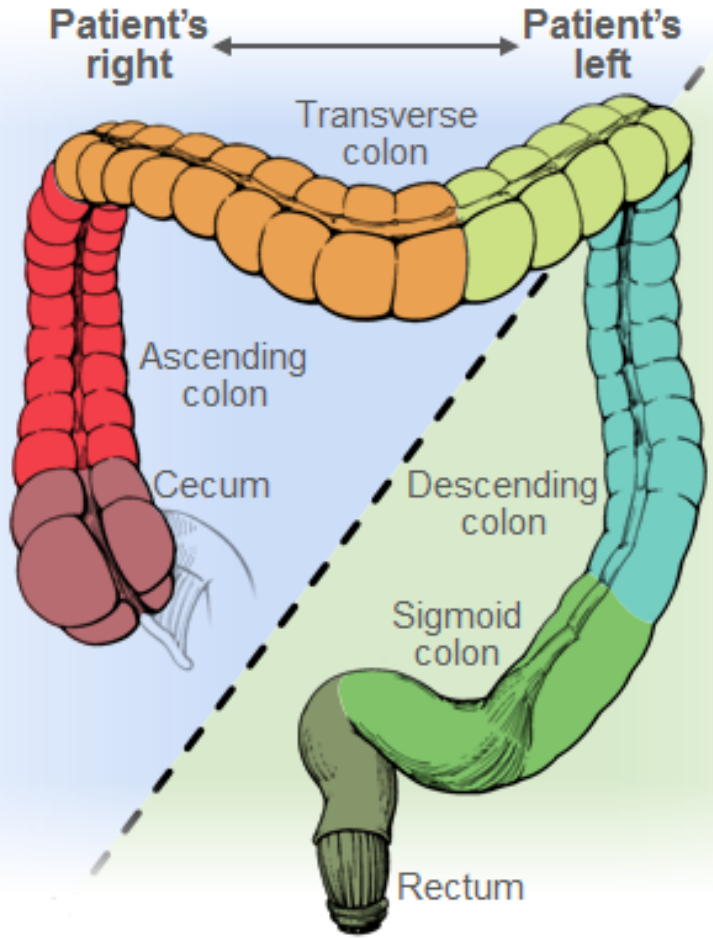
RIGHT vs. LEFT

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

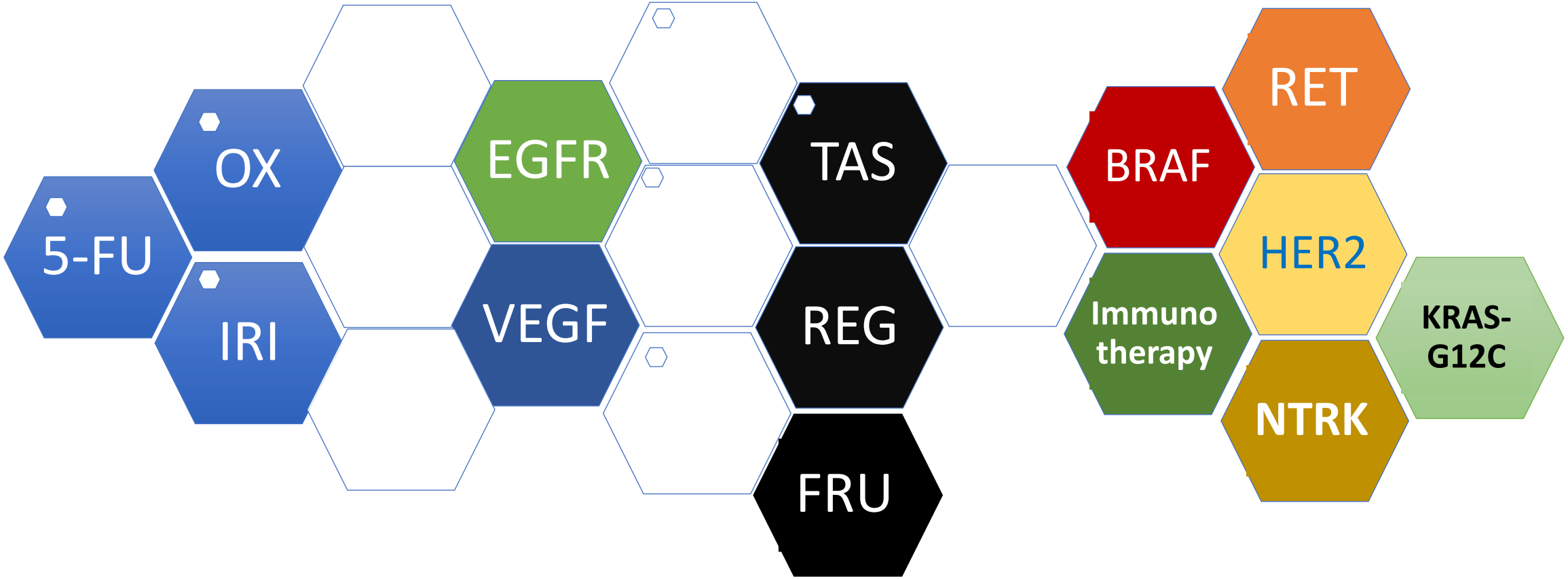
Overall BETTER prognosis

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

@pashtoonkasi

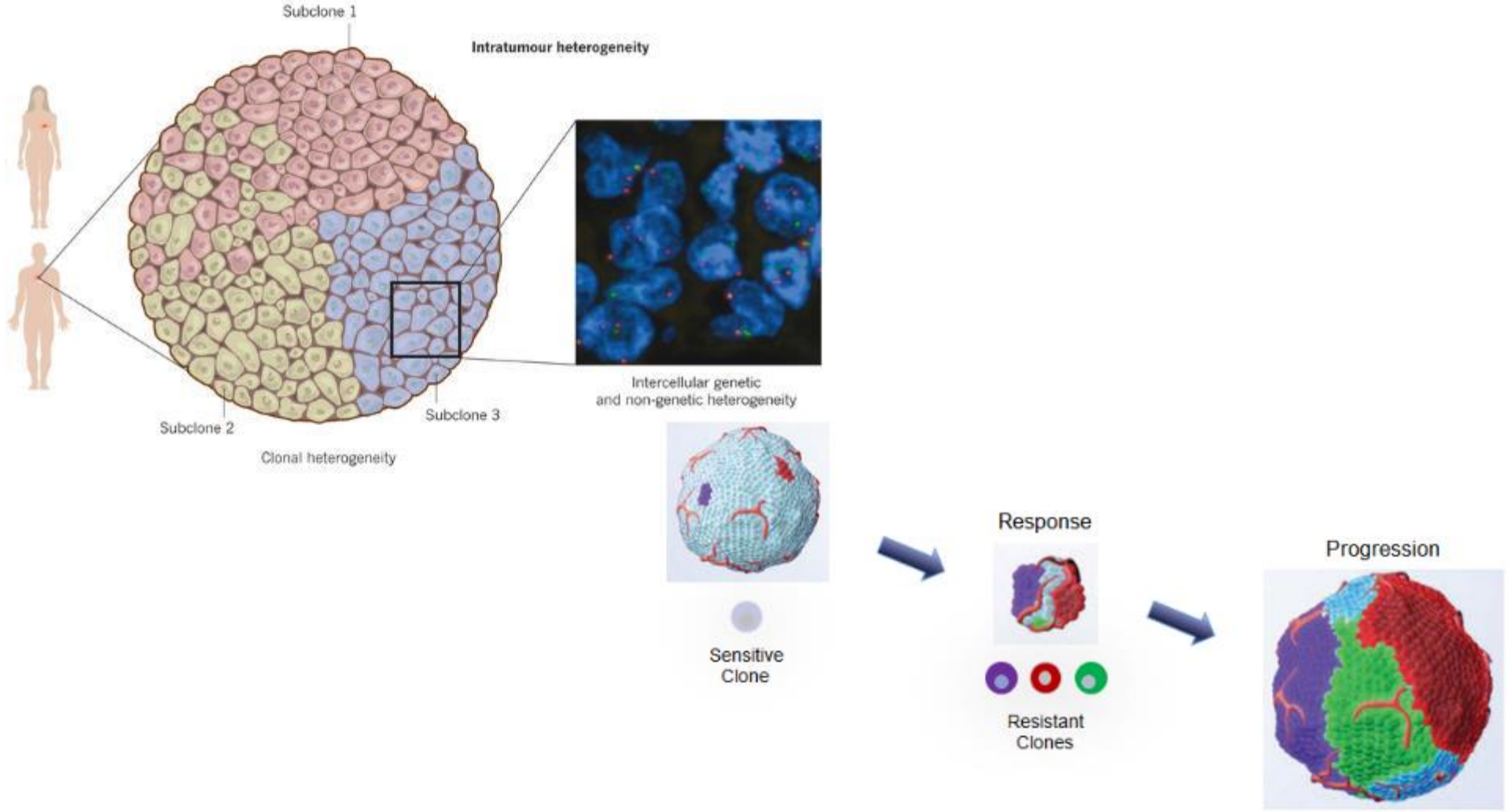
Kasi PM et al. Colorectal Cancer. Lancet Oct 2019.

Treatment options for patients with mCRC



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

Intratumoral and temporal heterogeneity



Burrell RA, et al. *Nature.* 2013;501:338.
Misale S, et al. *Cancer Discov*. 2014;4:1269.

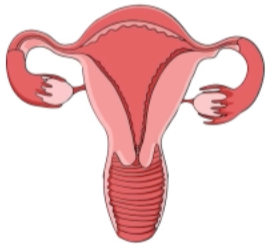
1st line metastatic setting

Liquid biopsy as a complimentary and adjunct tool to tissue testing

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

Frequency of tissue insufficiency

OVARIAN CANCER [1]

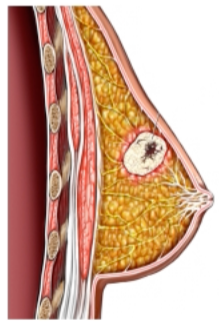


~10%

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.

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)**

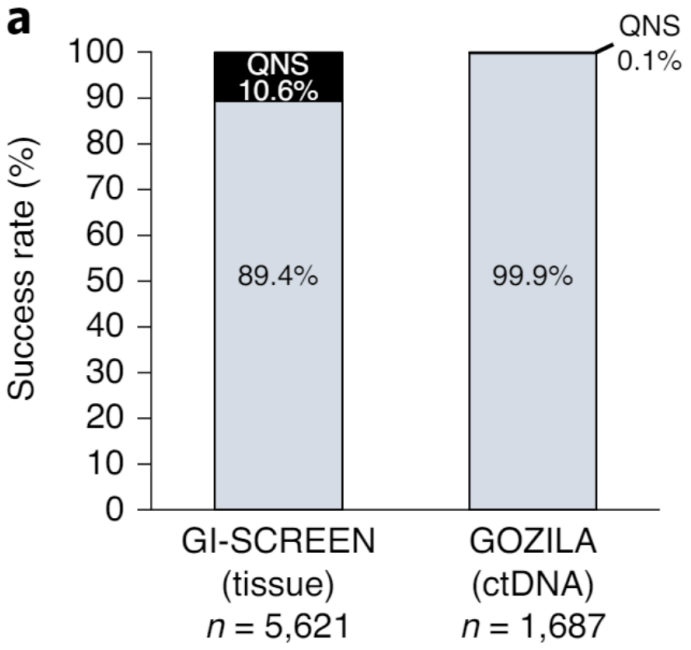
	Anti-EGFR OS (months)	Anti-VEGF OS (months)
NCDB	**42.9**	27.5
CALGB 80405	**39.3**	32.6
PEAK	**43.4**	32.0
FIRE-3	**38.3**	28.0
PARADIGM	**37.9**	34.7
PARADIGM (ctDNA hyper-selected)	**42.1**	35.5

Shitara K et al.
Negative hyperselection of patients with RAS wild-type metastatic colorectal cancer for panitumumab: A biomarker study of the phase III PARADIGM trial.
DOI: 10.1200/JCO.2023.41.4_suppl.11 Journal of Clinical Oncology 41, no. 4_suppl (February 01, 2023)

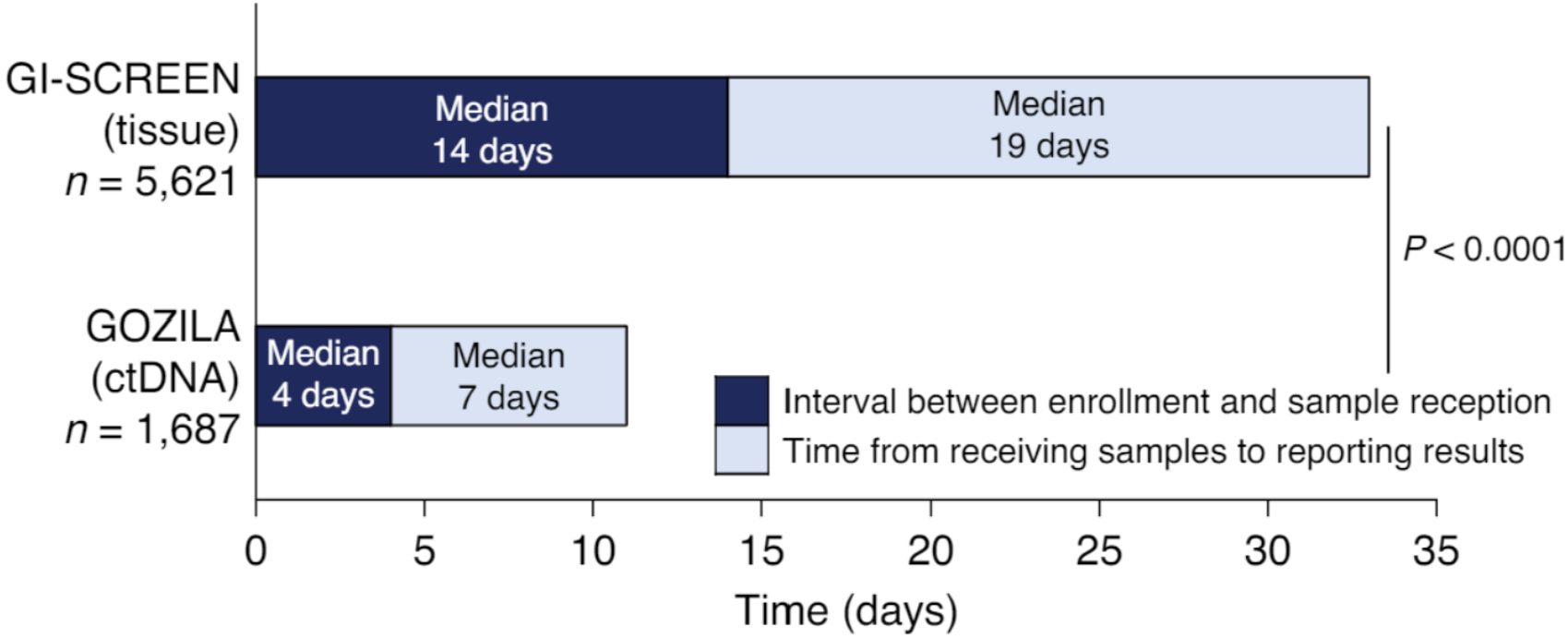
Potential Advantages of Using ctDNA Assays to Assess Actionable Mutations

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

Quantity Not Sufficient



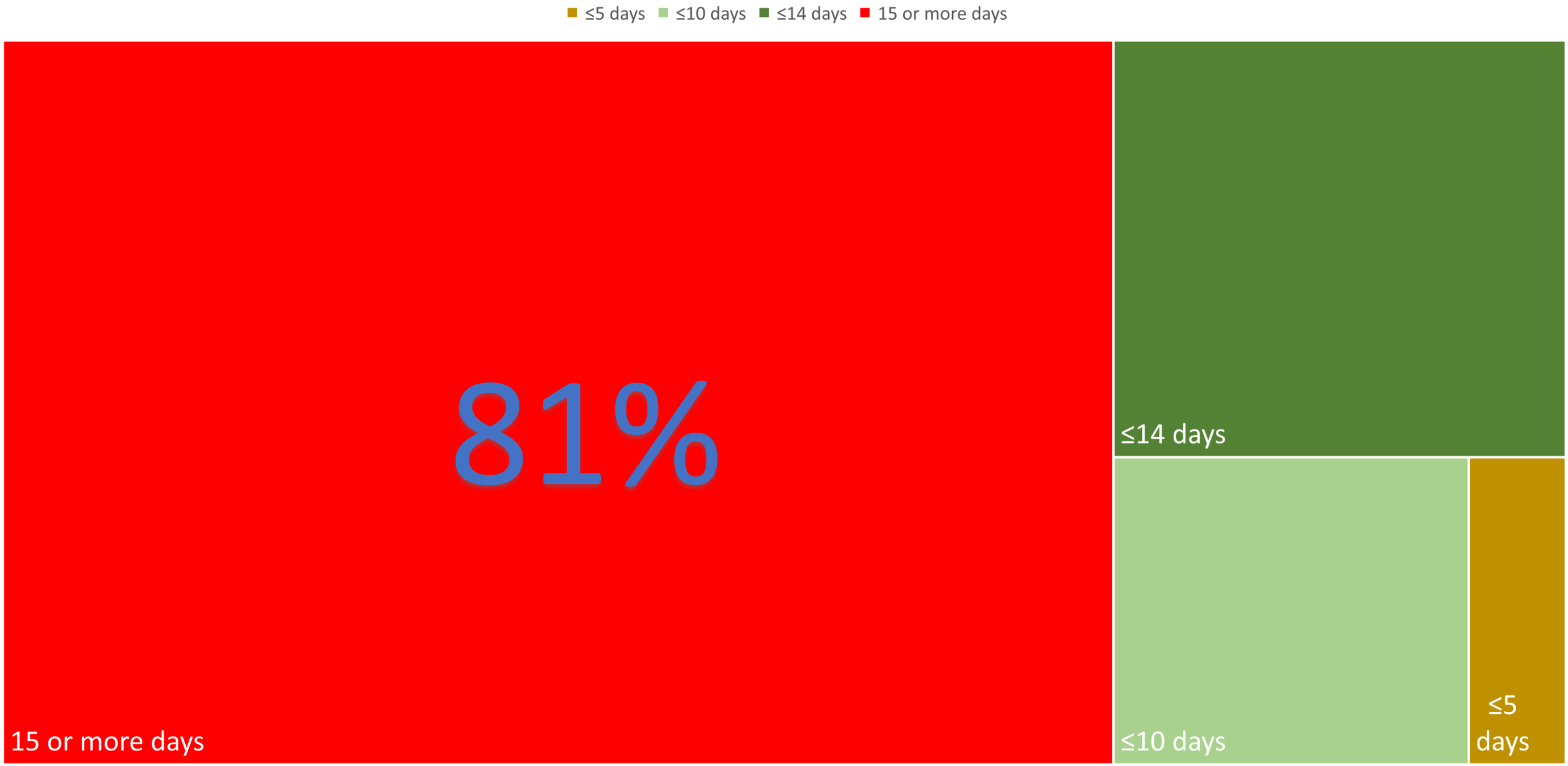
Turnaround time



Turnround time

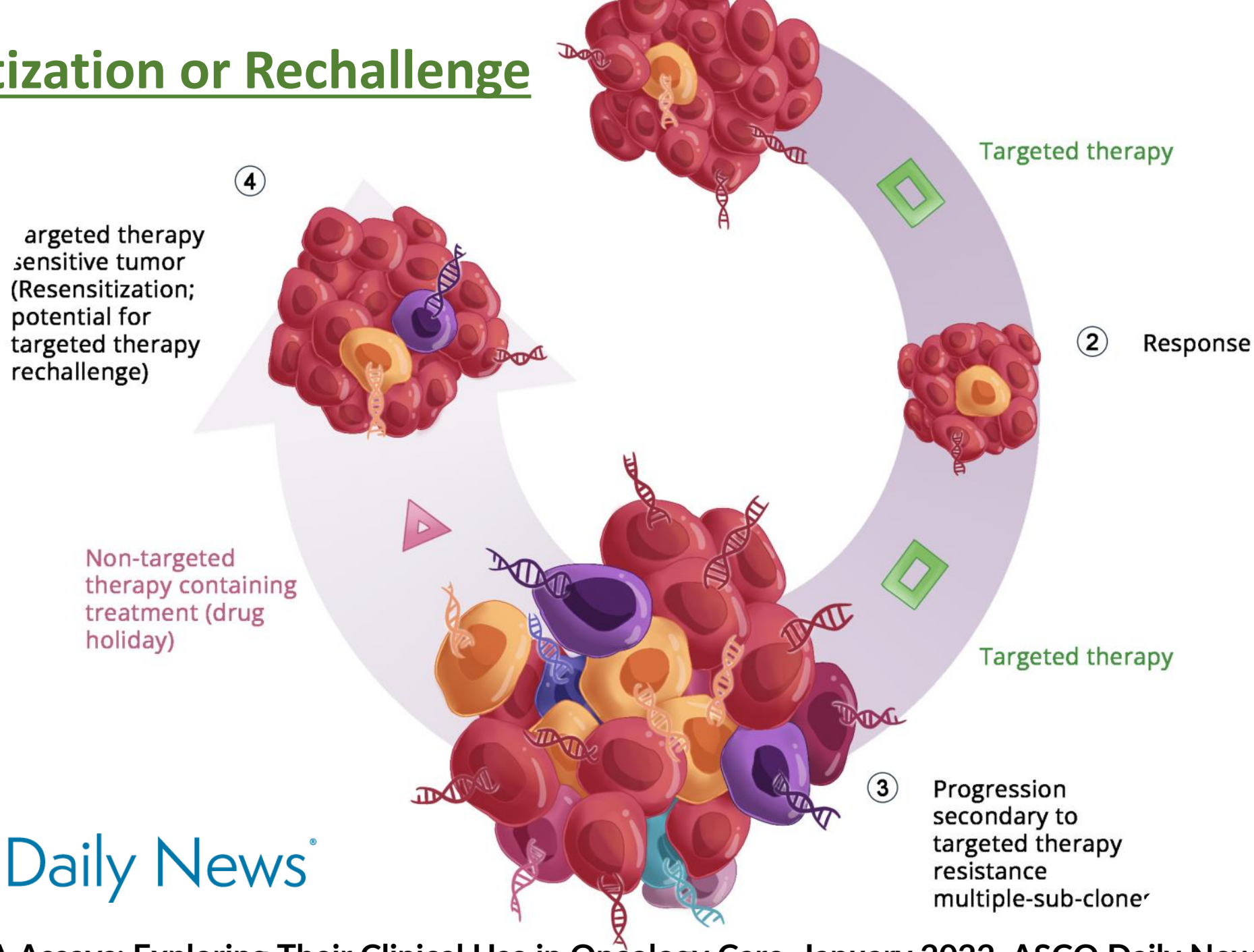
Nakamura. Nat Med. 2020;26:1859.

RAS-testing and turnaround times



Sangaré L, Delli-Zotti K, Florea A, Rehn M, Benson AB, Lowe KA. An evaluation of *RAS* testing among metastatic colorectal cancer patients in the USA. Future Oncol. 2021 May;17(13):1653-1663. PMID: 33629919.

Resensitization or Rechallenge



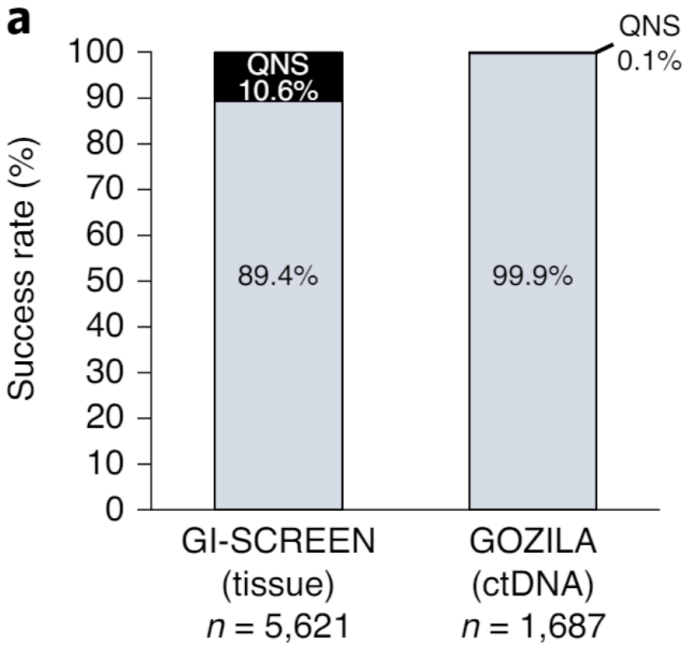
ASCO Daily News®

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

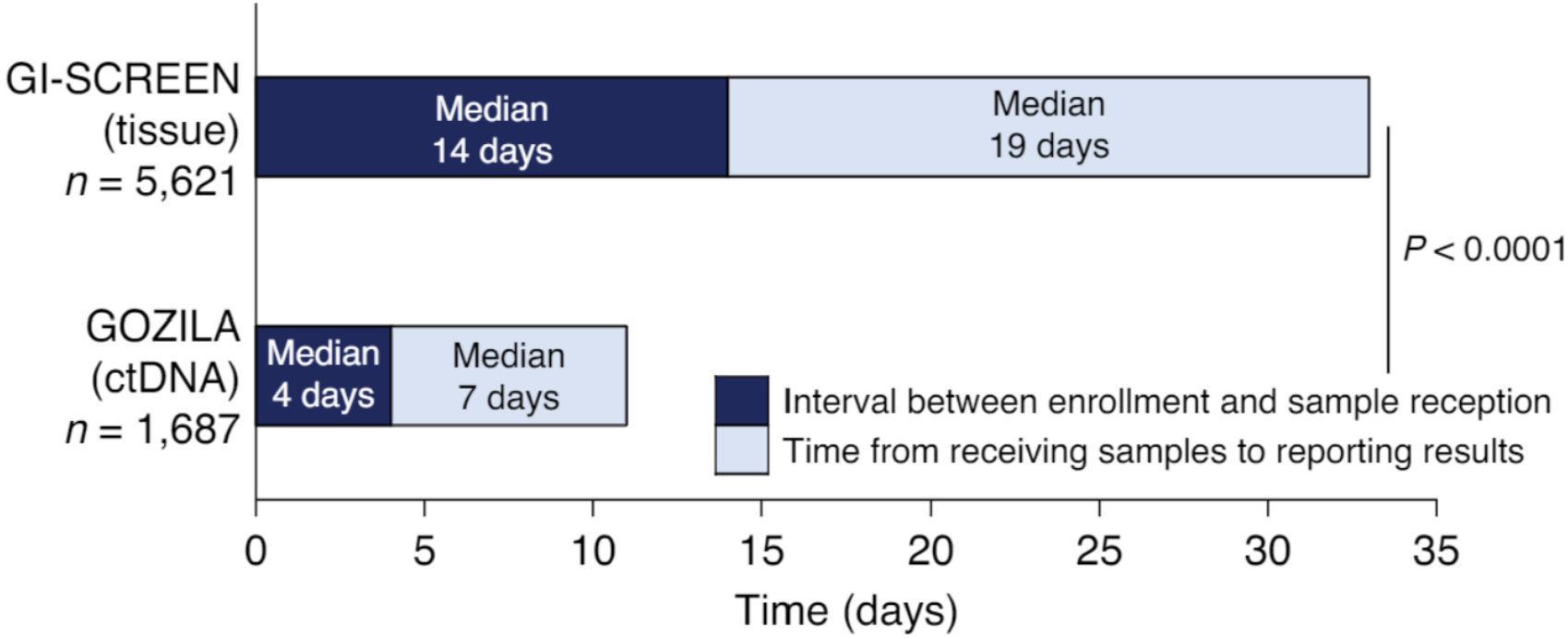
Potential Advantages of Using ctDNA Assays to Assess Actionable Mutations

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

Quantity Not Sufficient

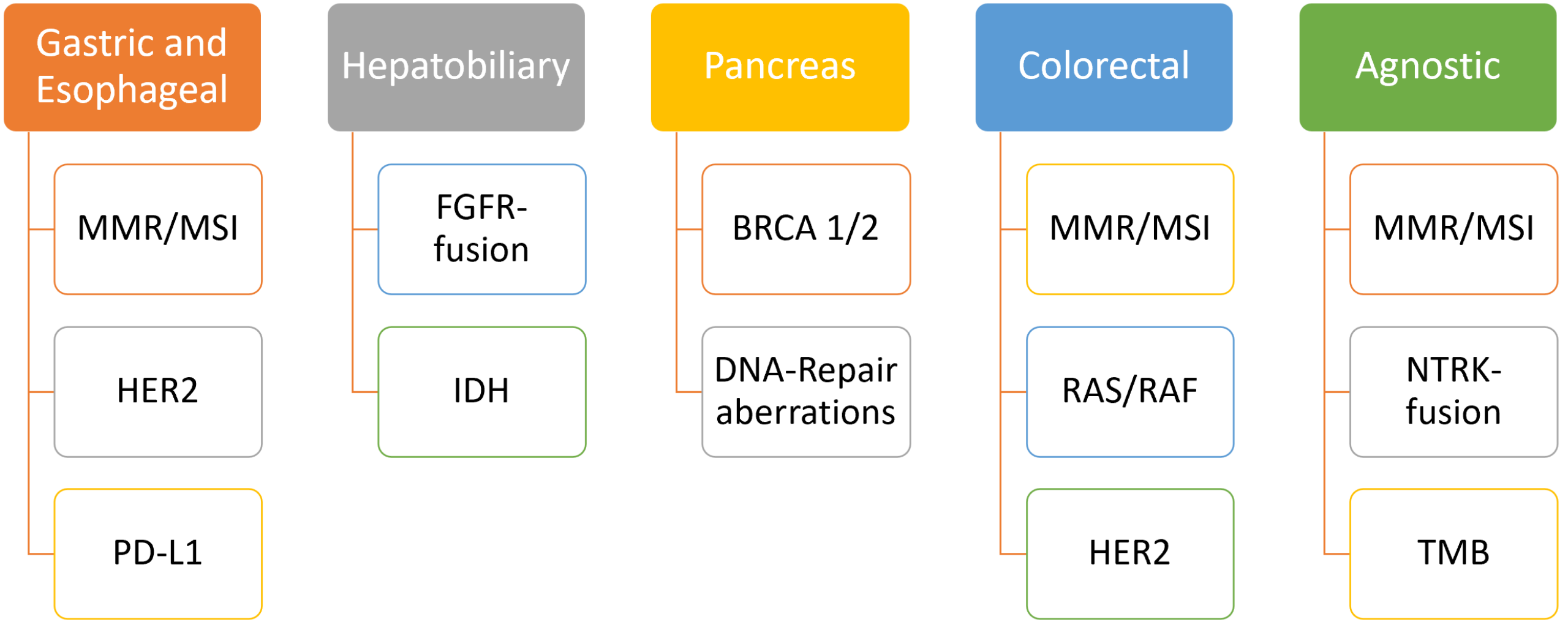


Turnaround time



Turnround time

Nakamura. Nat Med. 2020;26:1859.



Blood TMB or Liquid TMB (bTMB)

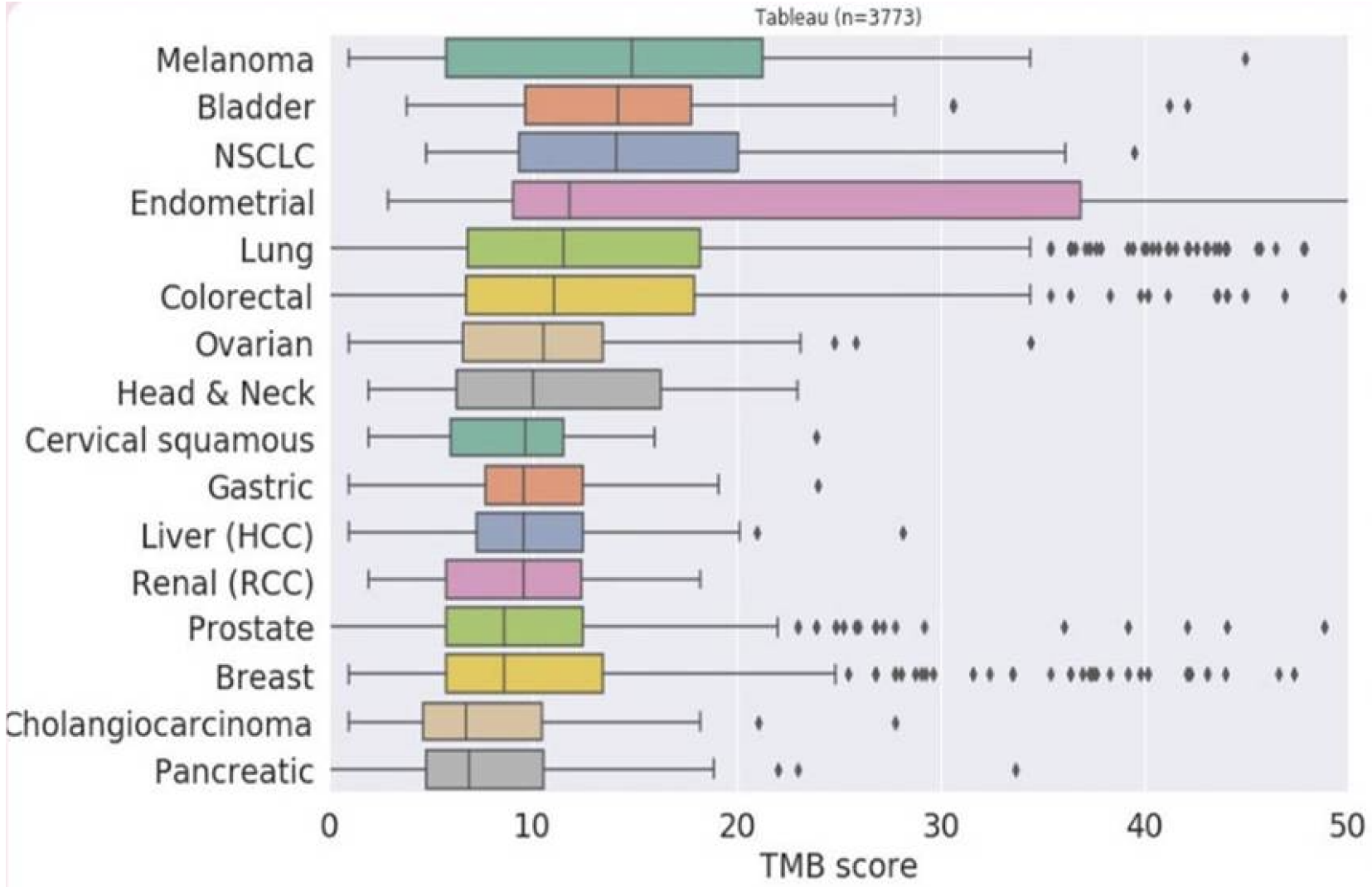
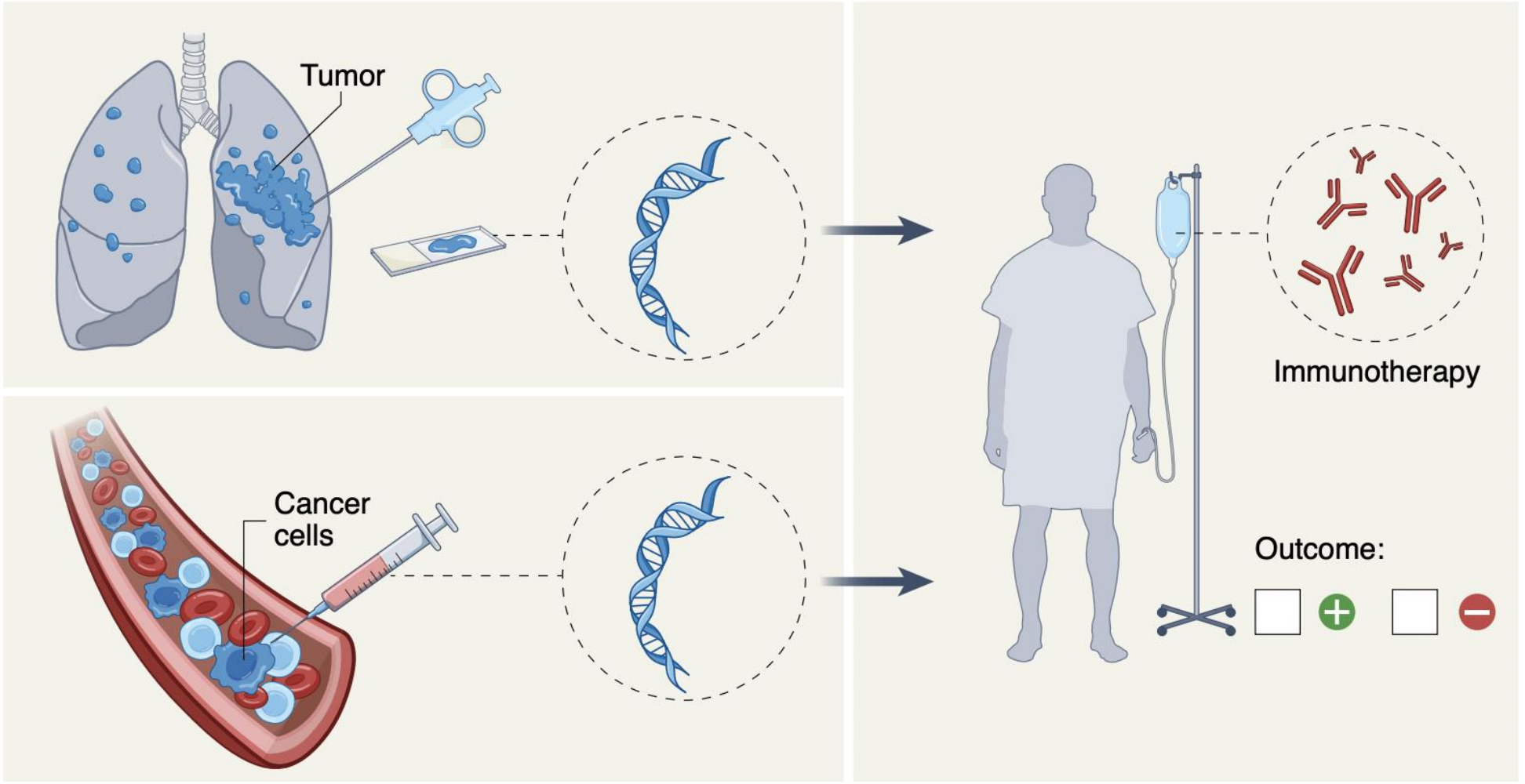


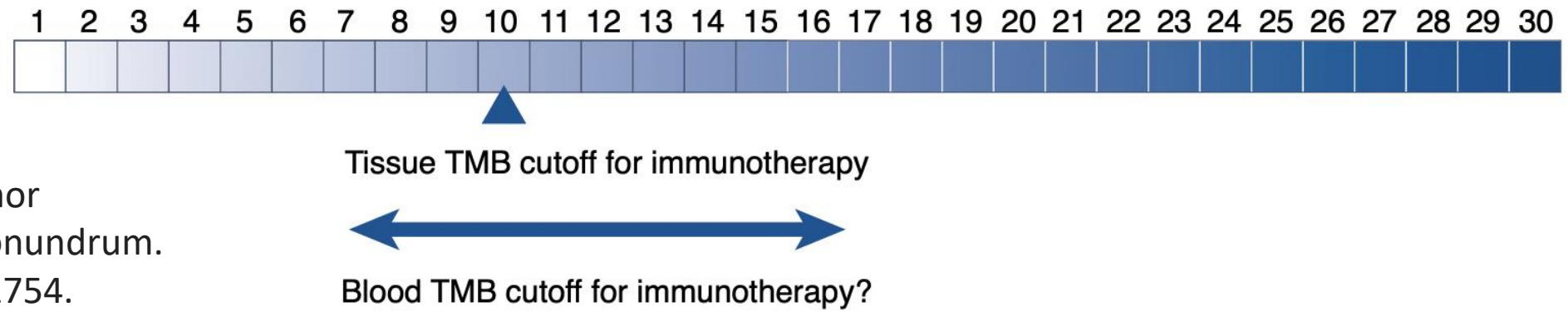
Figure 1: Distribution of blood TMB (bTMB) scores across solid tumors

	Tumor Type	Mean TMB	Median TMB	80th percenti
	NSCLC	14.35	11.48	20.19
Gastrointestinal	Colorectal	16.49	11.03	20.1
	Liver (HCC)	10.44	9.54	13.35
	Cholangiocarcinoma	10.07	6.7	10.53
	Pancreatic	15.25	6.85	11.36
	Gastric	12.29	9.57	13.82
Genitourinary	Bladder	17.18	14.16	20.1
	Renal (RCC)	9.06	9.57	13.14
	Prostate	12.2	8.61	13.4
Gynecological	Ovarian	11.79	10.53	14.98
	Endometrial	33.65	11.77	48.75
	Cervical squamous	9.81	9.64	13.59
Other	Breast	12.87	8.61	15.31
	Melanoma	20.19	14.83	23.79
	Head & Neck	13.31	9.99	17.41

Table 1: Distribution of TMB scores (defined as m

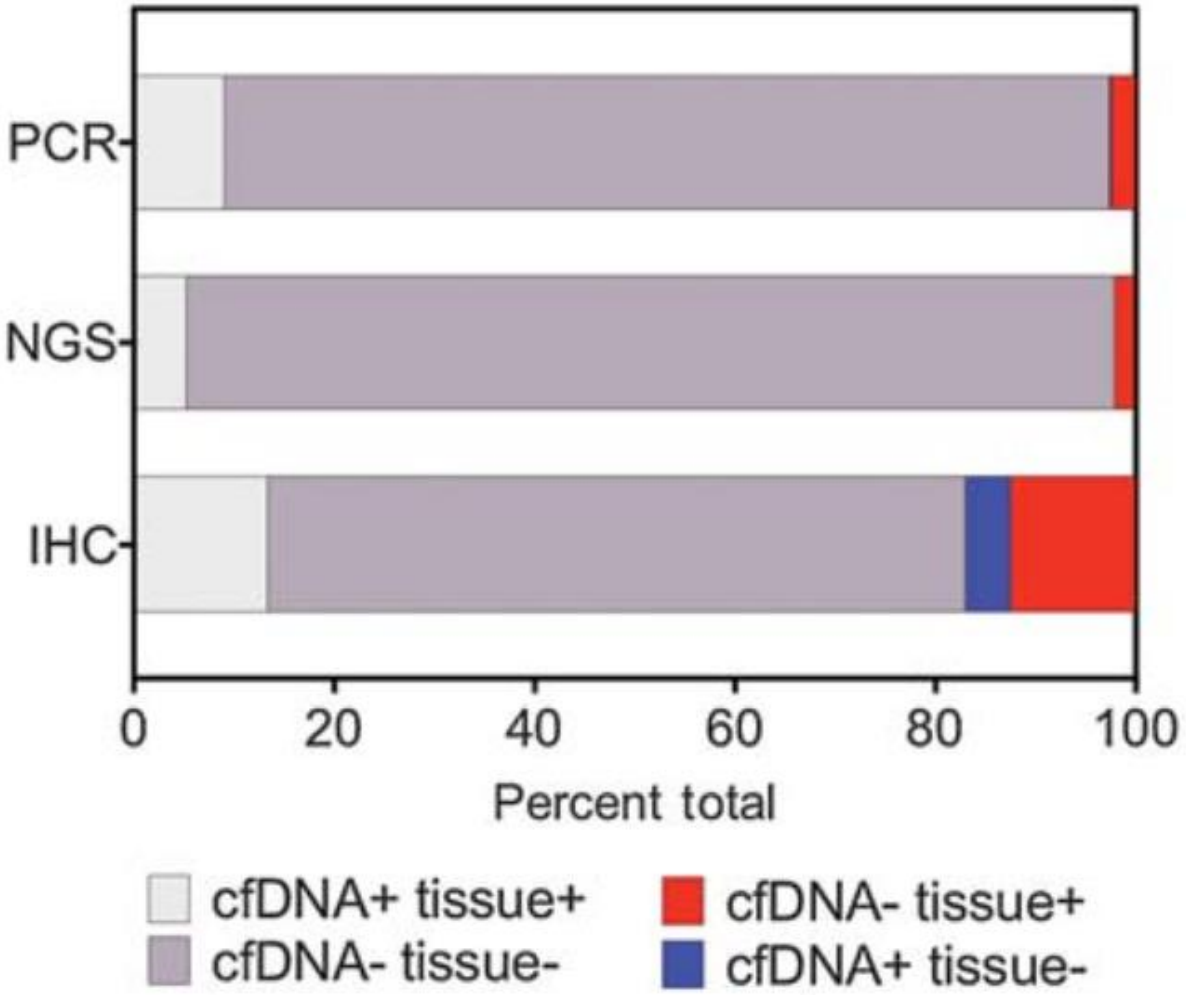
Blood versus tissue TMB cutoffs

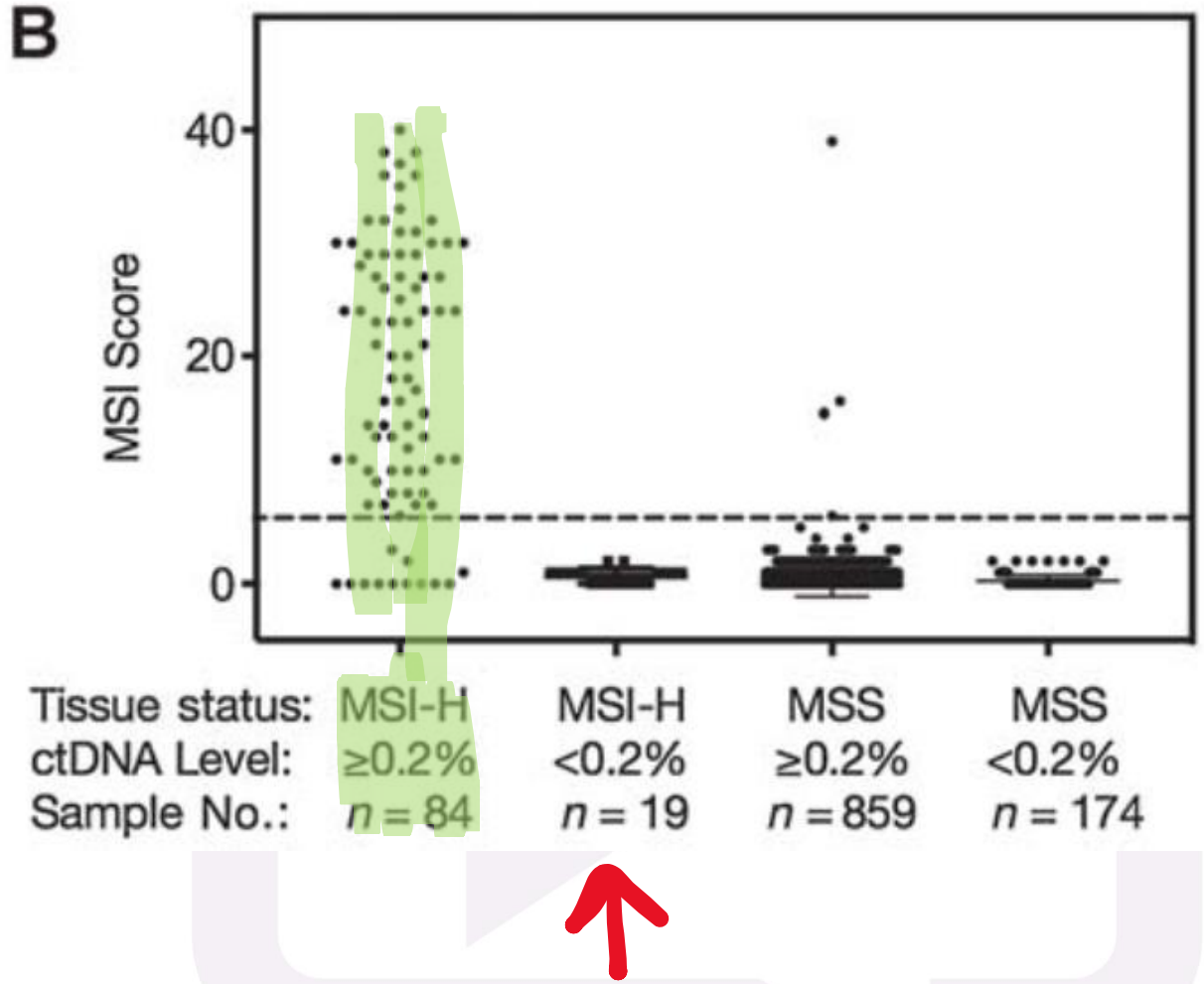




Kasi PM. Liquid biopsies and tumor mutational burden: the cutoff conundrum. Nat Med. 2022 Sep;28(9):1753-1754.

Microsatellite Instability - Plasma





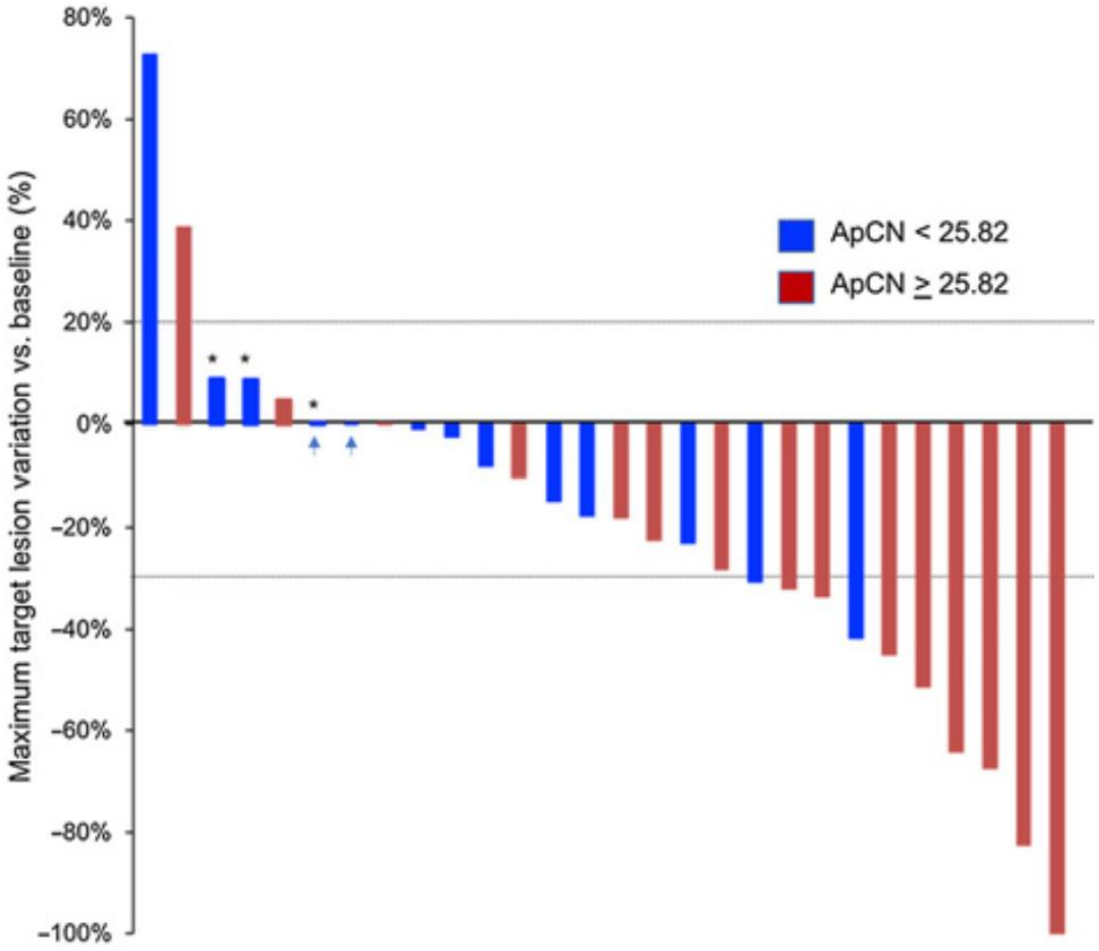
Validation of Microsatellite Instability Detection Using a Comprehensive Plasma-Based Genotyping Panel.
Clin Cancer Res. 2019 Dec 1;25(23):7035-7045. PMID: 31383735.

CLINICAL CANCER RESEARCH

HER2-targeted therapies in patients with HER2+ metastatic colorectal cancer

Regimen	Trial (n) – year	ORR	PFS	OS	Most common Grade 3+ AEs
Trastuzumab + lapatinib	HERACLES-A (n=32) – 2016	**28%**	**4.7m**	**10m**	Fatigue 16% Decreased LVEF 6%
Trastuzumab + pertuzumab	MyPathway (n=84; 57 evaluable) – 2019	**32%**	**2.9m**	**11.5m**	Hypokalemia 5% Abdominal pain 5%
Pertuzumab and T-DM1	HERACLES-B (n=31) – 2020	**9.7%**	**4.1m**	**Not reported**	Thrombocytopenia 7%
Trastuzumab deruxtecan	DESTINY-CRC01 (N=78; 53 HER2+) – 2021	**45.3%**	**6.9m**	**15.5m**	Neutropenia 15% Anemia 13%
Tucatinib + trastuzumab	MOUNTAINEER (n=117) *FDA Approved	**38.1%**	**8.2m**	**24.1m**	Hypertension 7% Diarrhea 3.5%

HER2/ERBB2 - Plasma

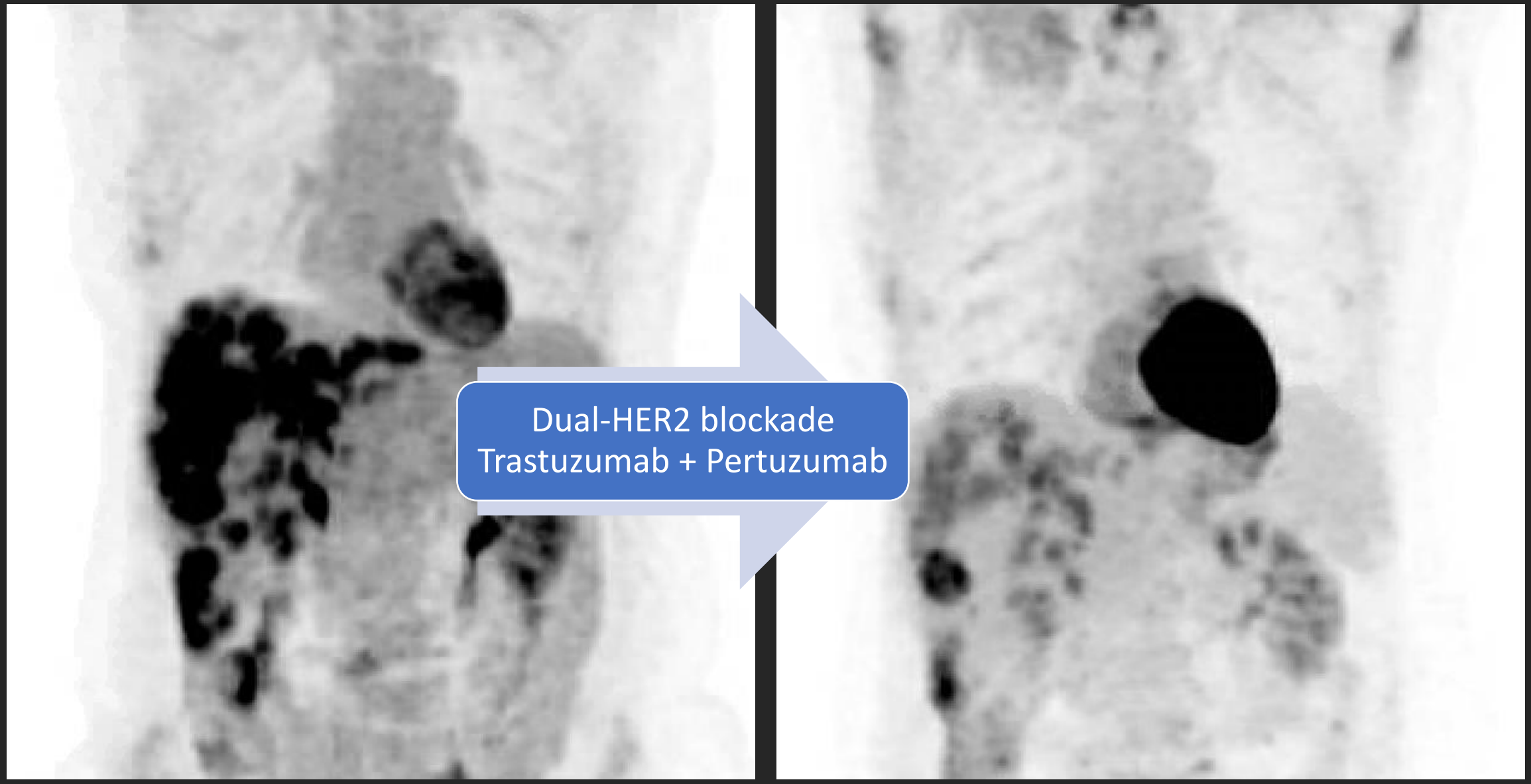


Results:

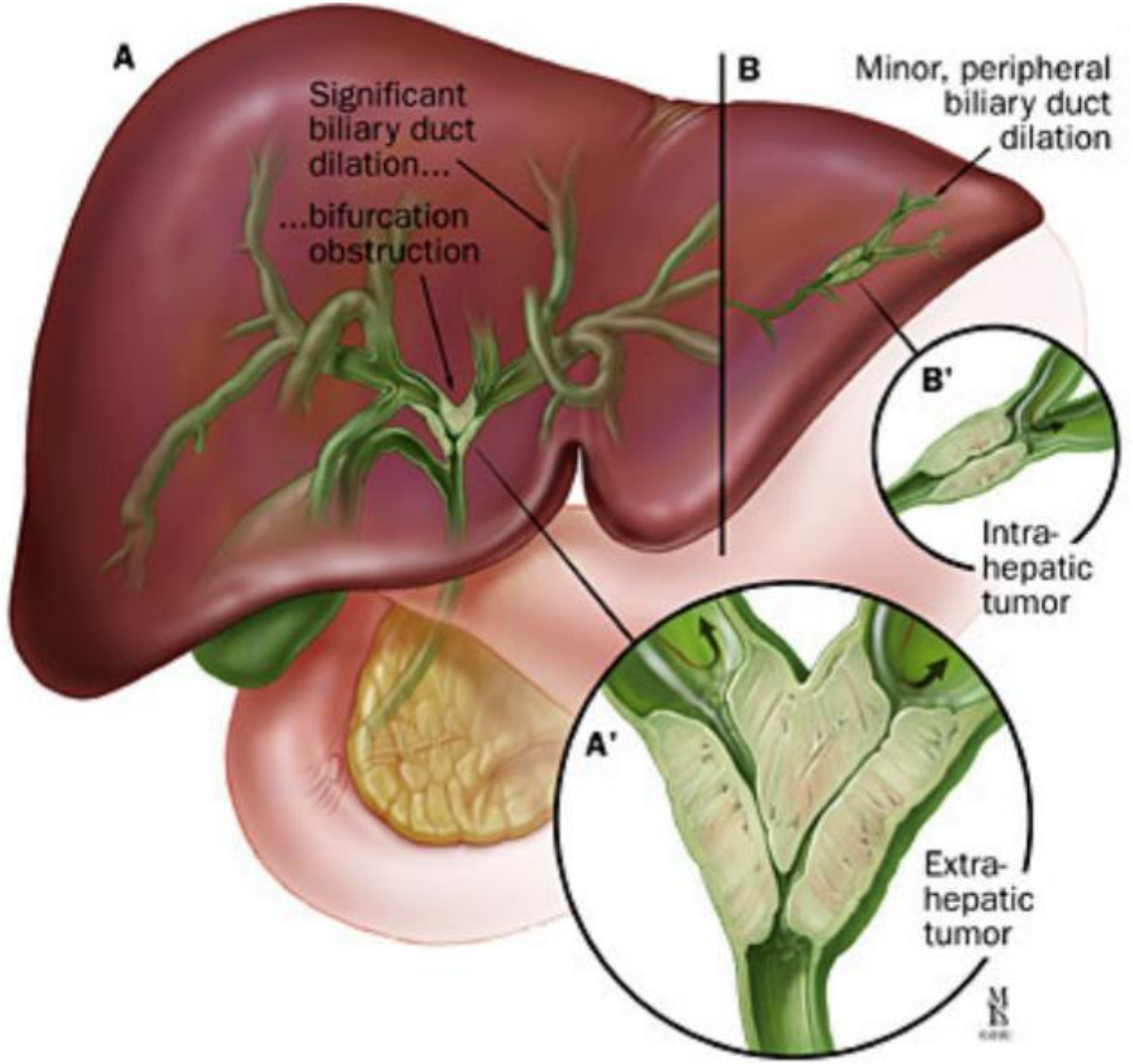
- 47 of 48 samples had detectable ctDNA
- **46 of 47 samples were ERBB2-amplified** on the basis of cfDNA [2.55–122 copies];
- **97.9% sensitivity** (95 CI, 87.2%–99.8%)].
- An adjusted ERBB2 pCN of 25.82 copies correlated with ORR and PFS (P = 0.0347)

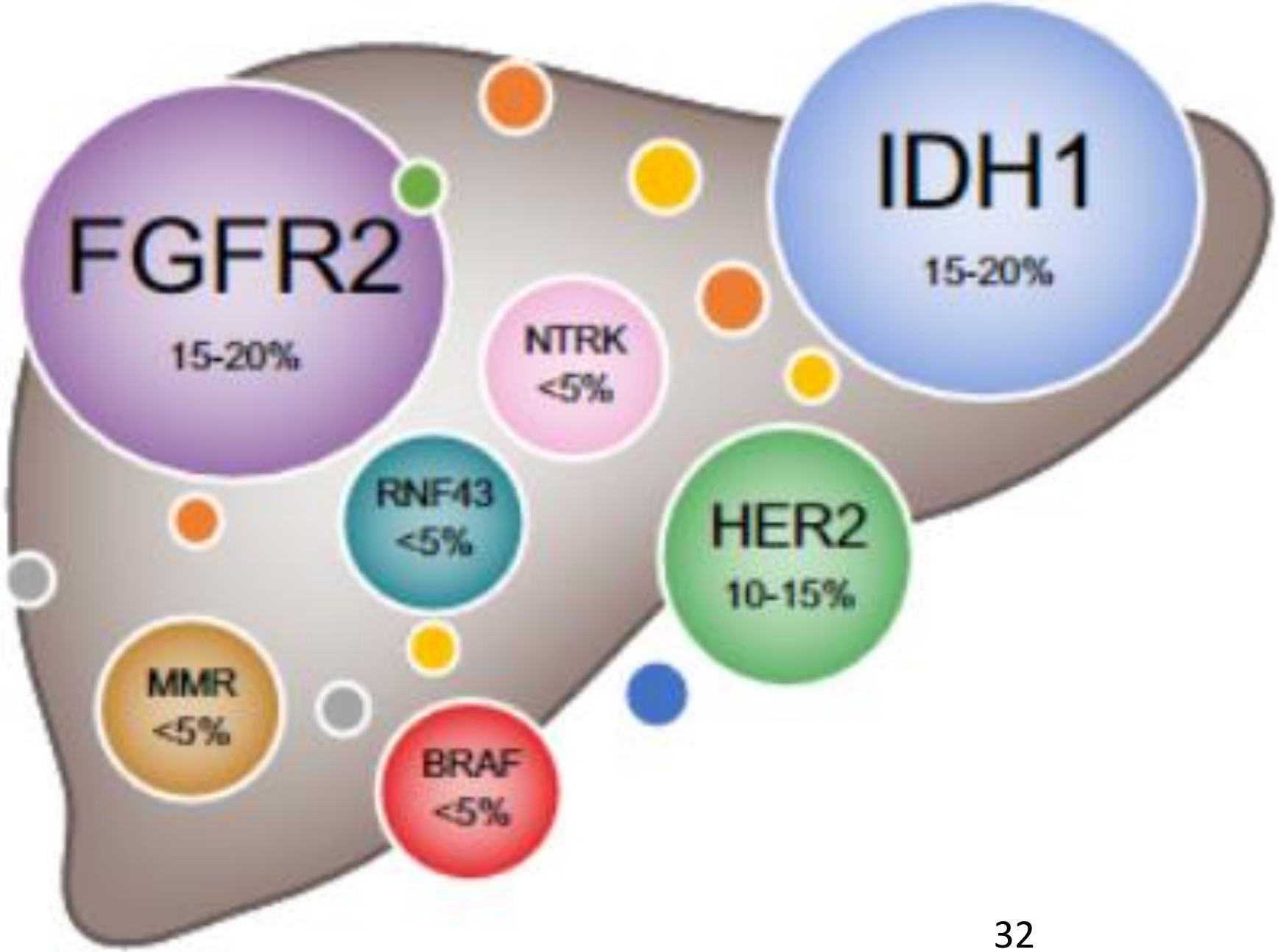
Plasma HER2 (*ERBB2*) Copy Number Predicts Response to HER2-targeted Therapy in Metastatic Colorectal Cancer.
Clin Cancer Res. 2019 May 15;25(10):3046-3053. PMID: 30808777.

CLINICAL CANCER RESEARCH

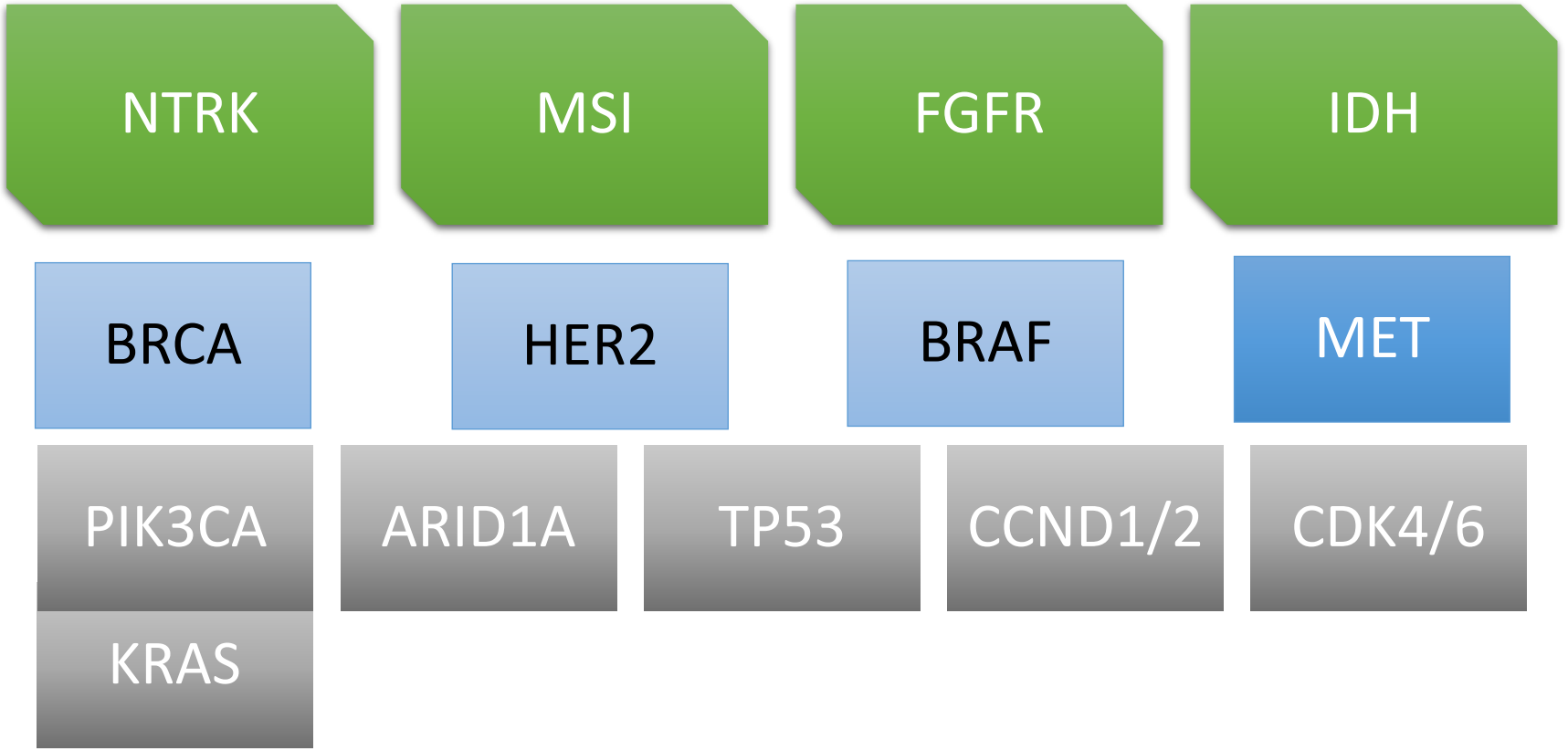

Dual-HER2 blockade
Trastuzumab + Pertuzumab

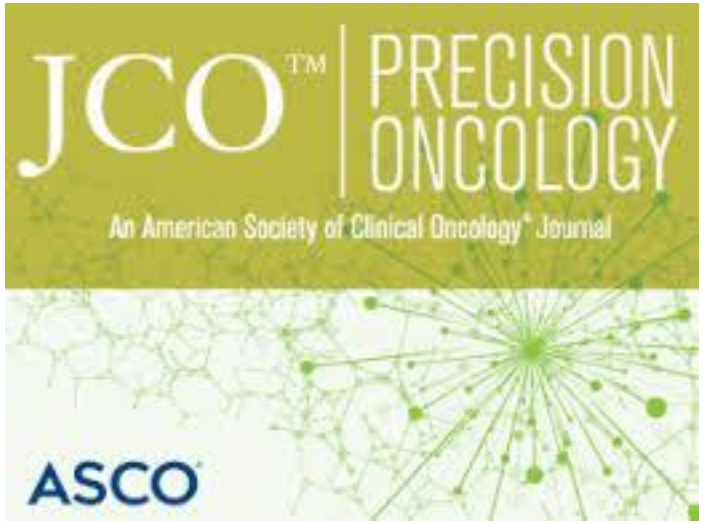
Cholangiocarcinoma: Target-rich disease




FGFR2
15-20%
IDH1
15-20%
NTRK
<5%
RNF43
<5%
HER2
10-15%
MMR
<5%
BRAF
<5%

Real-time circulating tumor DNA profiling of advanced cholangiocarcinoma (CCA)

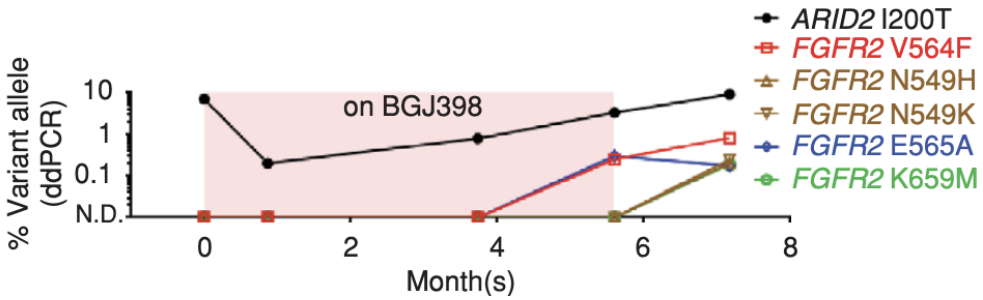




Kasi PM et al. JCO PO January 2019 & Journal of Clinical Oncology 36, no. 15_suppl (May 2018) 4089-4089.

	Tissue	*Liquid*	*Combined*
FGFR2 fusions	3.40%	11.30%	6.80%
IDH1/2	8.10%	7.50%	8.40%
BRAF V600E	1.00%	3.00%	2.50%
HER2	3.80%	-	3.00%
MET	1.30%	-	0.70%
BRCA1/2/ATM	2.60%	-	2.00%
PIK3CA	3.00%	8.80%	4.70%
ERRFI1	-	2.50%	0.70%
Total actionable	***23.20%***	***33.10%***	***28.80%***

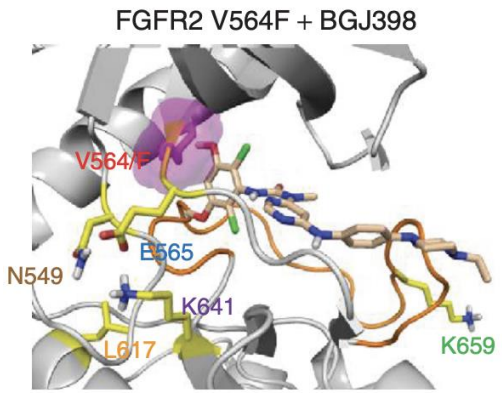
Kasi PM et al. ASCO GI 2021. Comparative landscape of actionable somatic alterations in advanced cholangiocarcinoma from circulating tumor and tissue-based DNA profiling.

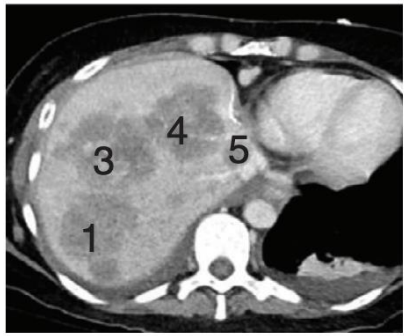


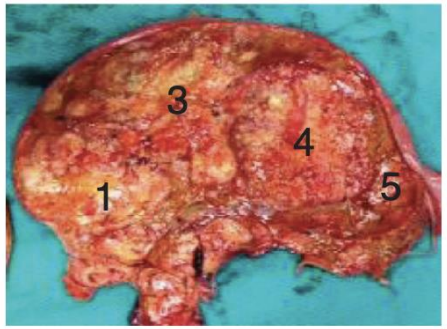
RESEARCH BRIEF

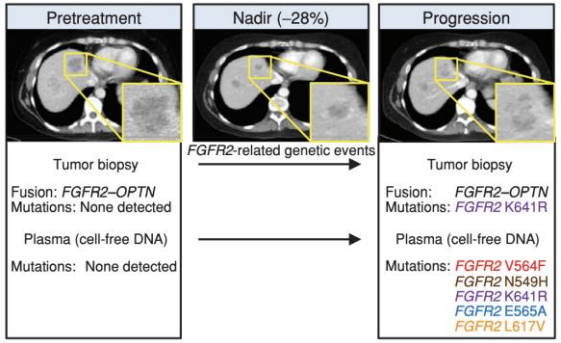
Polyclonal Secondary *FGFR2* Mutations Drive Acquired Resistance to FGFR Inhibition in Patients with FGFR2 Fusion–Positive Cholangiocarcinoma

252 | CANCER DISCOVERY MARCH 2017









Can we reliably use ctDNA kinetics?

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

ctDNA as a rapid surrogate of tumor response

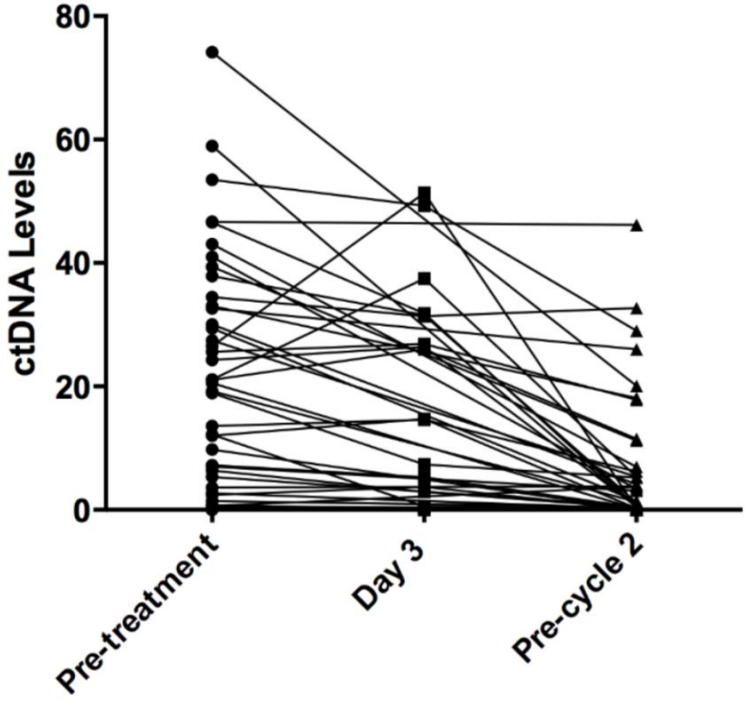
Half-life of ctDNA in circulation is measured in minutes/hours

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

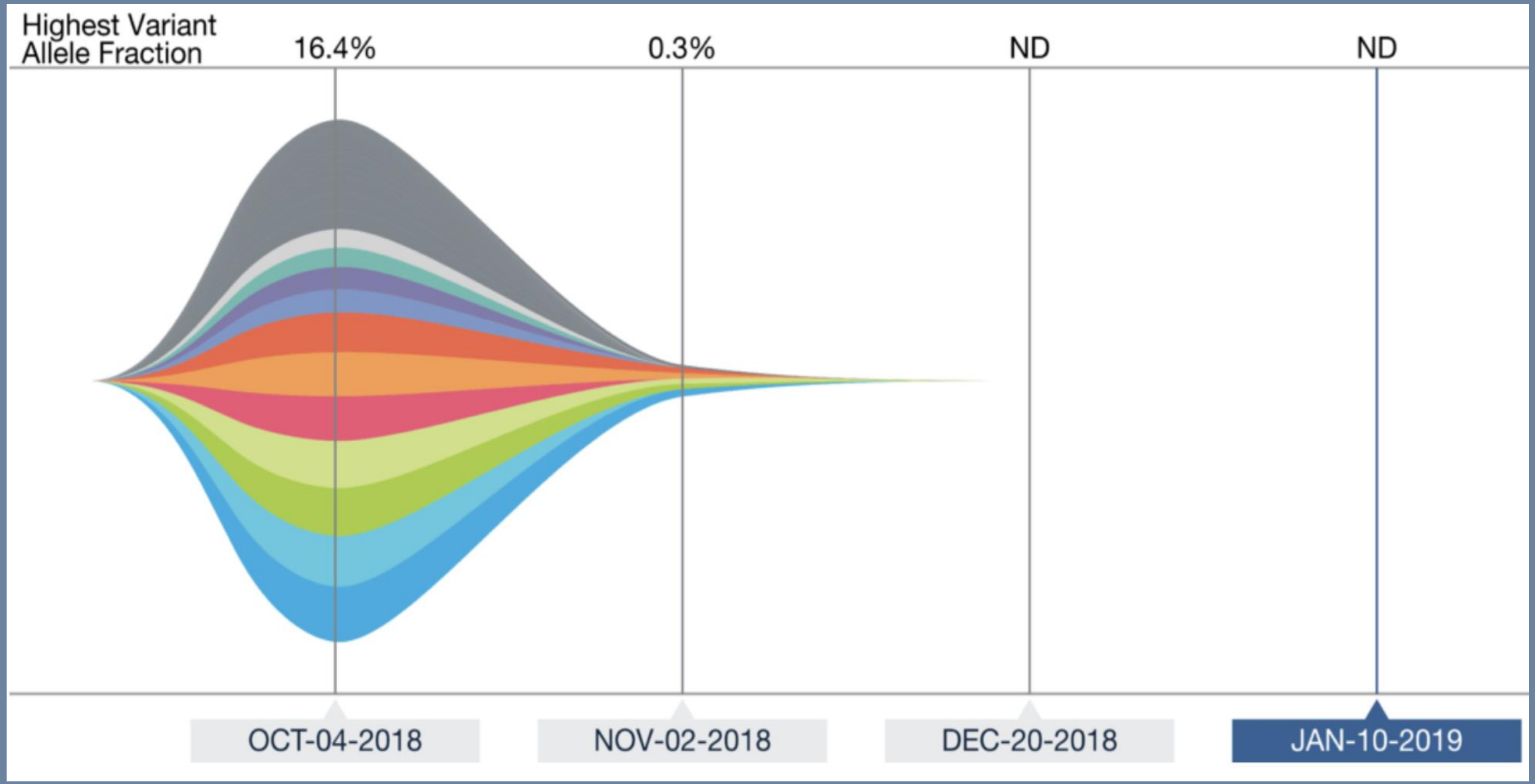
Similar findings also seen in urinary ctDNA.

Husain et al CCR ‘17

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

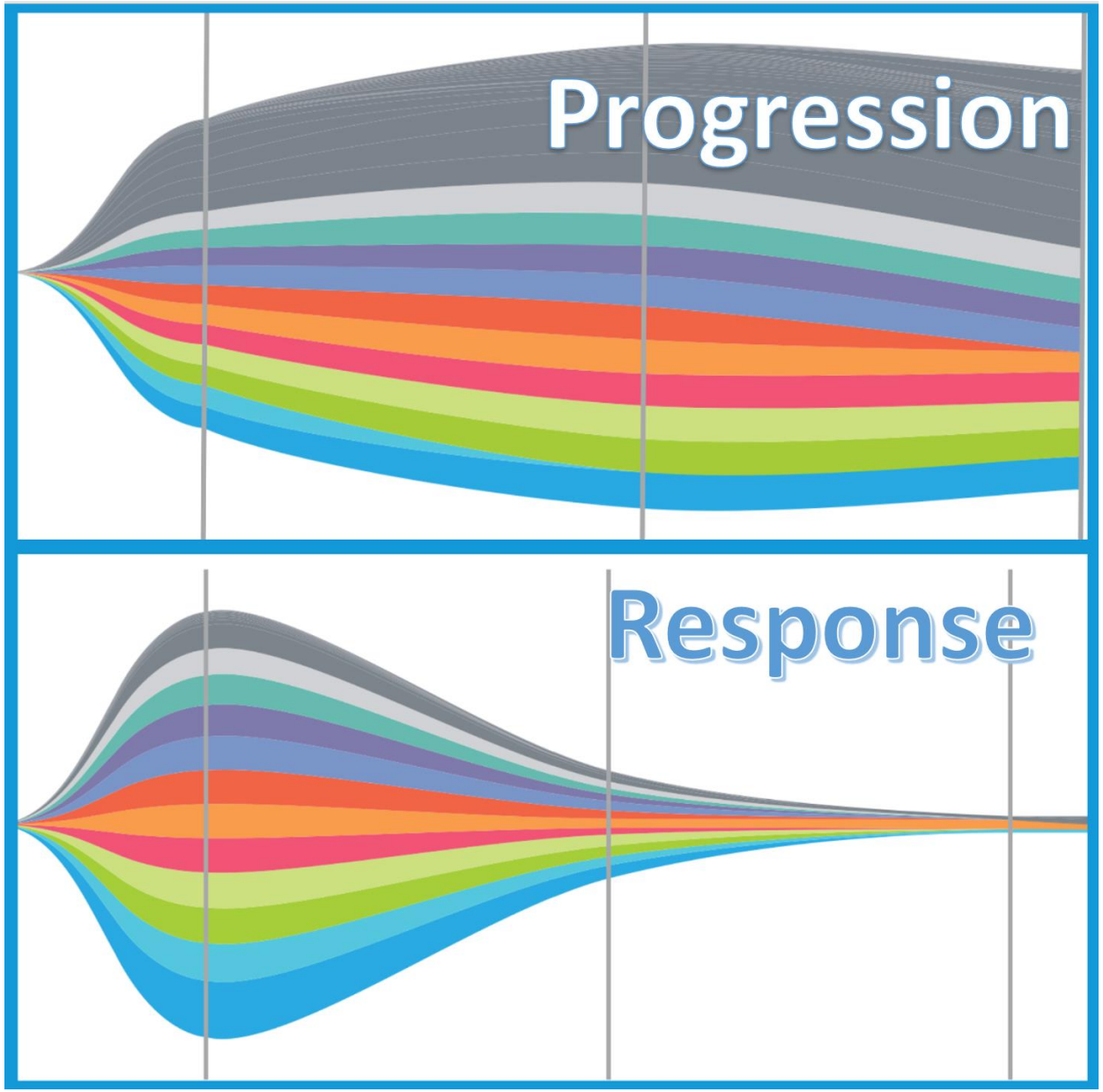


Tie et al Annals Oncology ‘15


Highest Variant Allele Fraction
16.4%
0.3%
ND
ND
OCT-04-2018
NOV-02-2018
DEC-20-2018
JAN-10-2019

Circulating tumor DNA and plasma microsatellite instability during PD-1 blockade

J Gastrointest Oncol Aug 17 2020; 11(4):826-828

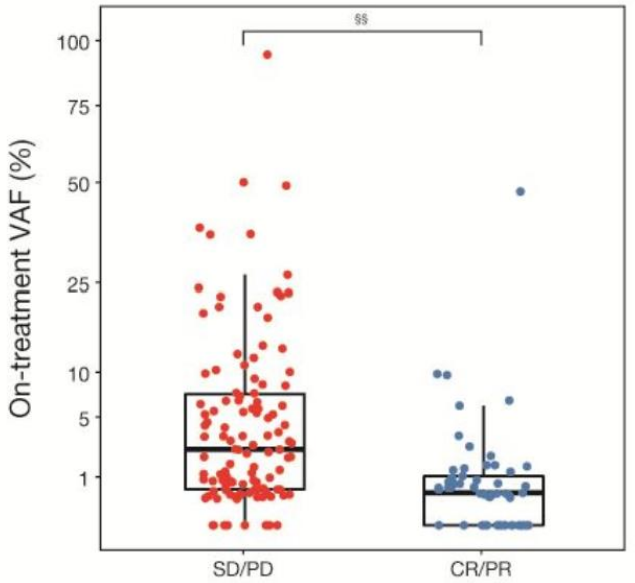


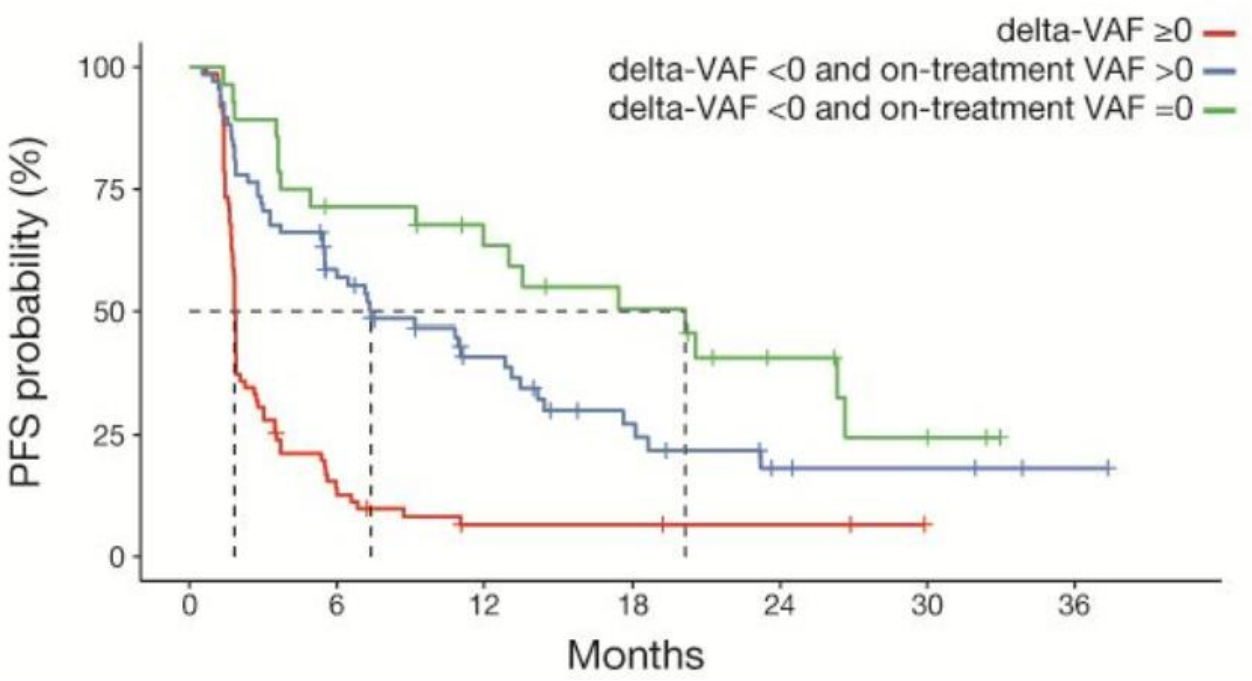
Circulating tumor DNA and plasma microsatellite instability during PD-1 blockade

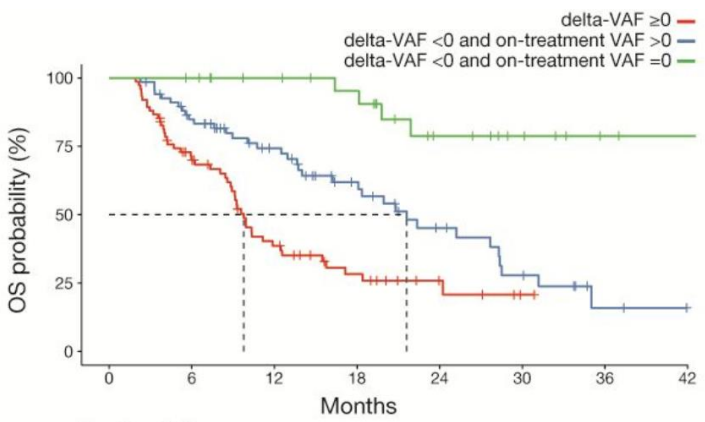
		Baseline	Week2	Week3	Week4	Week6	Week8	Week10	Week12	Imaging
Patient 1 – MSI-High Pancreas	CtDNA Highest VAF	0.7%			ND		ND		ND	**Response**
	MSI-High Plasma	+			X		X		X	
Patient 2 – MSI-High CRC	CtDNA Highest VAF	0.4%				ND				**Response**
	MSI-High Plasma	+				X				
Patient 3 – MSI-High CRC	CtDNA Highest VAF	0.7%					ND			**Response**
	MSI-High Plasma	+					X			
Patient 4 – MSI-High Gastric	CtDNA Highest VAF	16.4%			0.3%			ND	ND	**Response**
	MSI-High Plasma	+			+			X	X	
Patient 5 – MSI-High CRC	CtDNA Highest VAF	42.2%		0.6%				0.9%		**Response**
	MSI-High Plasma	+		+				X		
Patient 6 – MSI-High Esophageal	CtDNA Highest VAF	ND							ND	**Response**
	MSI-High Plasma	+							X	
Patient 7 – MSI-High CRC	CtDNA Highest VAF	31.2%		4.4%				0.3%		**Response**
	MSI-High Plasma	+		+				+		
Patient 8 – MSI-High CRC	CtDNA Highest VAF	11.7%		20.9%		18.1%				**Progression**
	MSI-High Plasma	+		+		+				
Patient 9 – MSI-High CRC	CtDNA Highest VAF	0.2%							0.8%	**Progression**
	MSI-High Plasma	+							+	
Patient 10 – MSI-High CRC	CtDNA Highest VAF	4.4%	2%					10.5%		**Progression**
	MSI-High Plasma	+	+					+		
Patient 11 – MSI-High CRC	CtDNA Highest VAF	0.2%		ND		0.3%			0.6%	**Progression**
	MSI-High Plasma	+		+		+			+	
Patient 12 – MSI-High CRC	CtDNA Highest VAF	2.4%		2.7%		1.7%				**Progression**
	MSI-High Plasma	+		+		+				

CANCER DISCOVERY

August 14, 2020

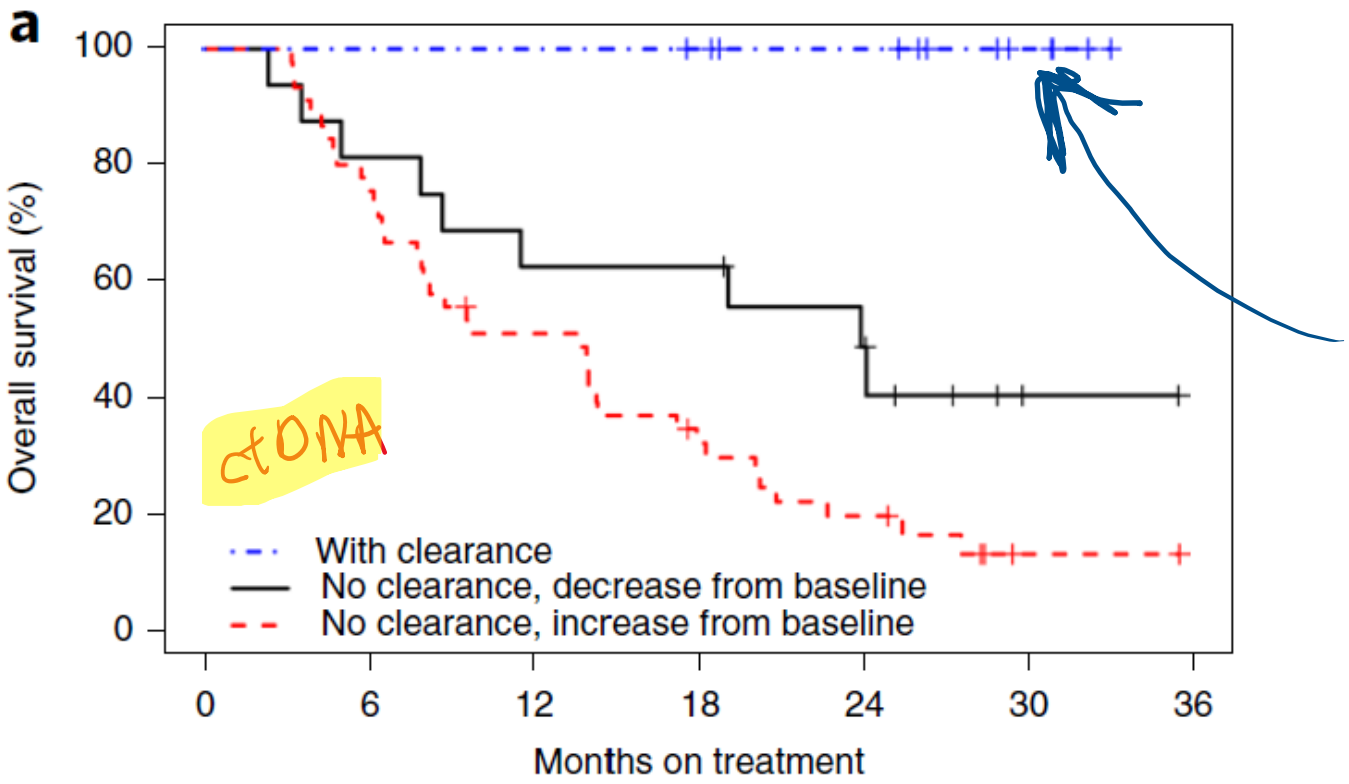


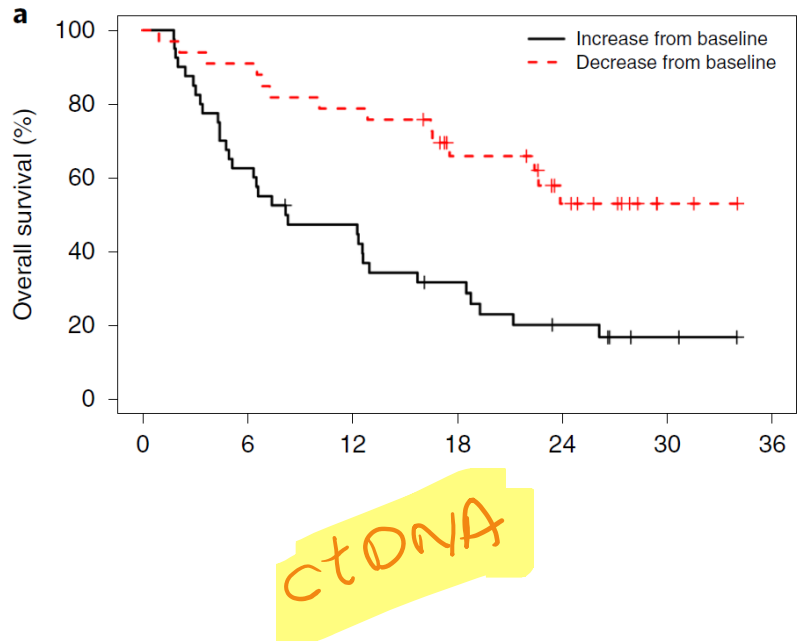


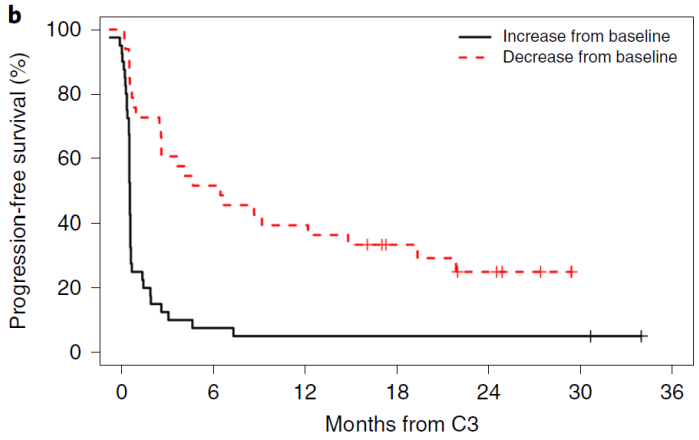


nature cancer

03 August 2020







ASCO Daily News®

Kinetics of Liquid Biopsies in Predicting Response to Immunotherapy

October 1, 2020

Pashtoon M. Kasi, MD, MS

@pashtoonkasi

“MRD”

Platforms and updates

Tumor heterogeneity “Shedding”

Cannot forget biology; high shedders versus low shedders

Precision Medicine and Imaging

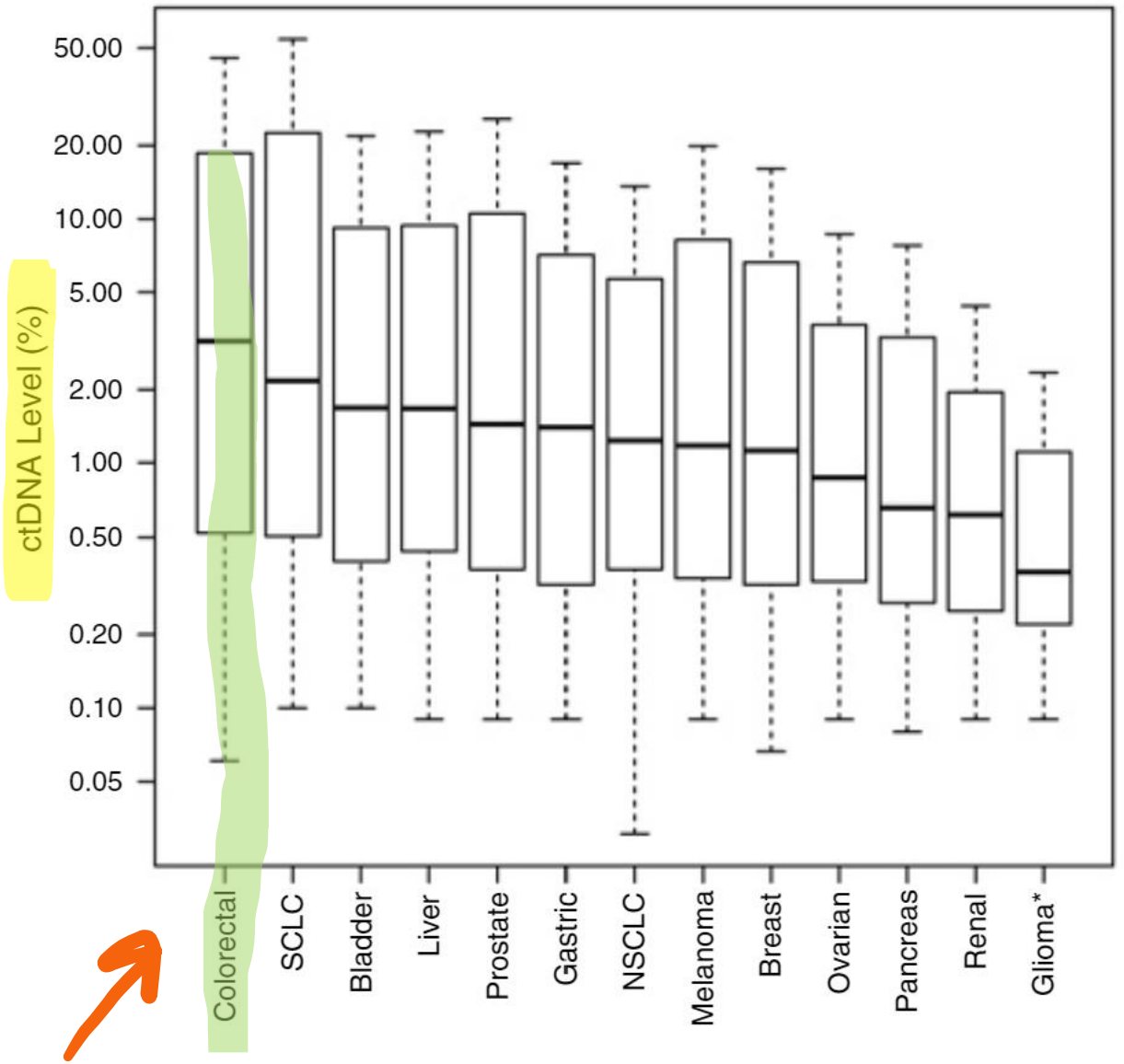
Clinical Cancer Research

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]

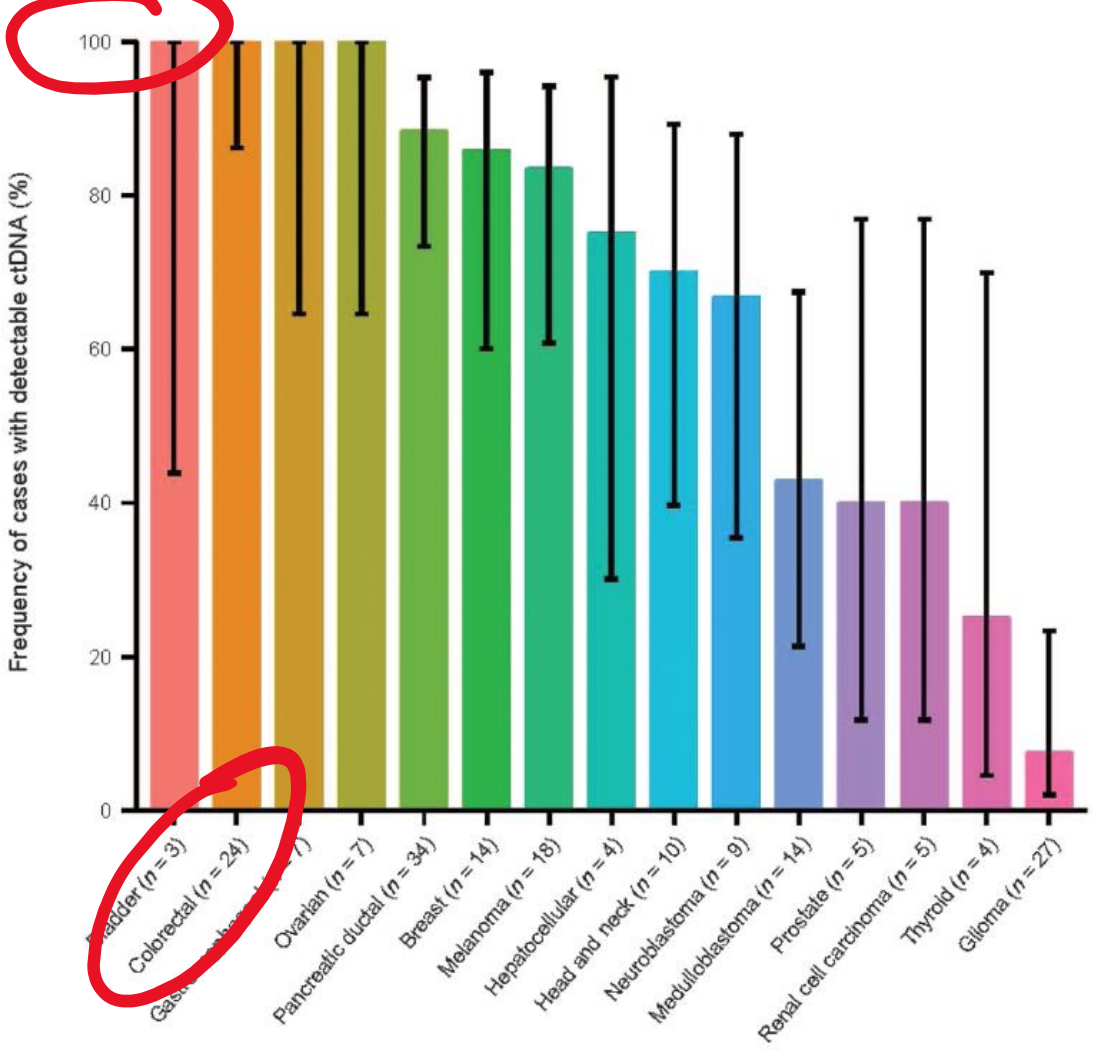
Clinical Cancer Research

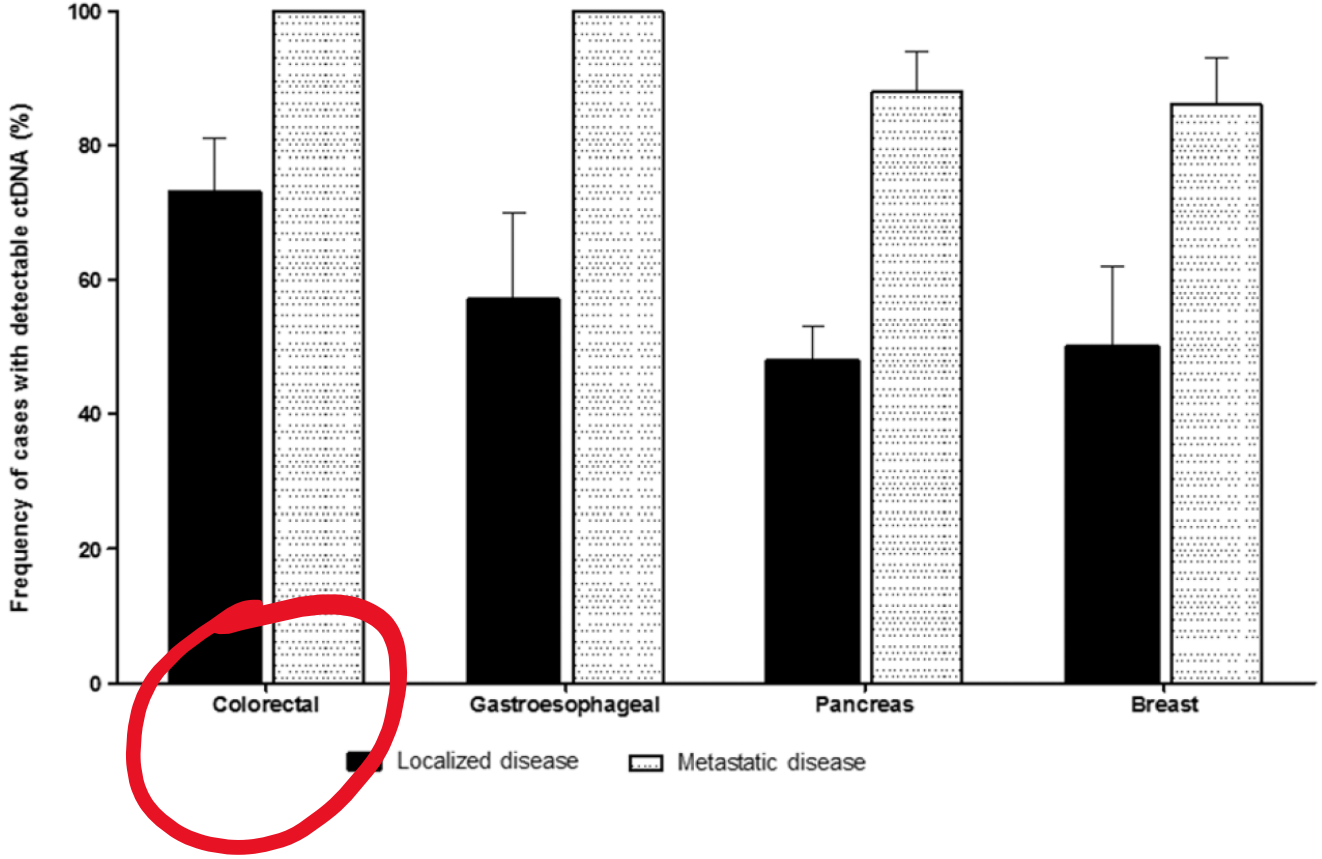
August 2018
Volume 24, Issue 15



@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)

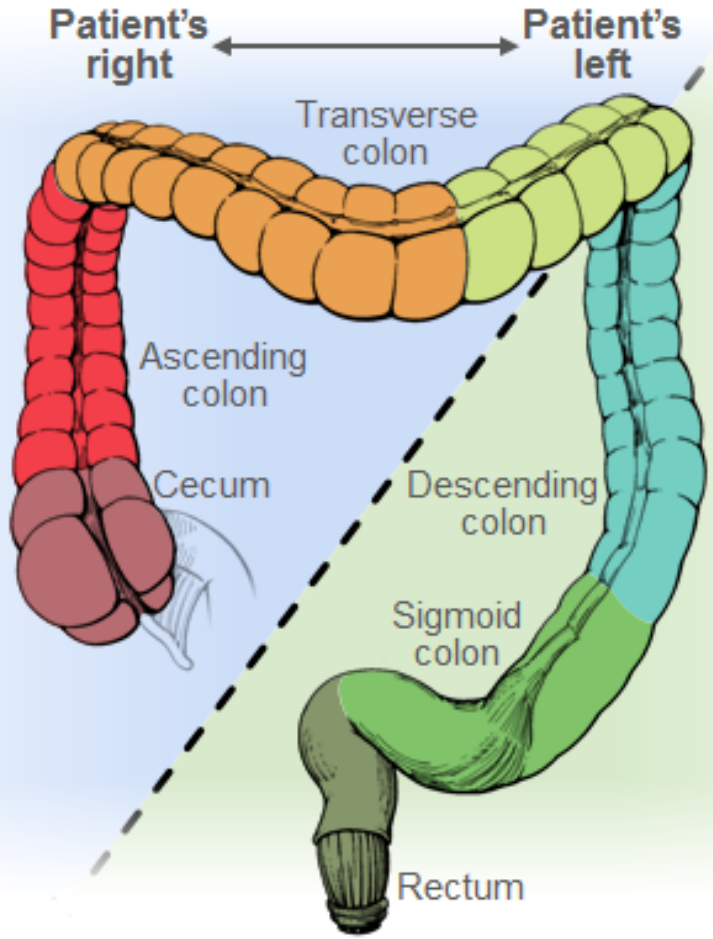
RIGHT vs. LEFT

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

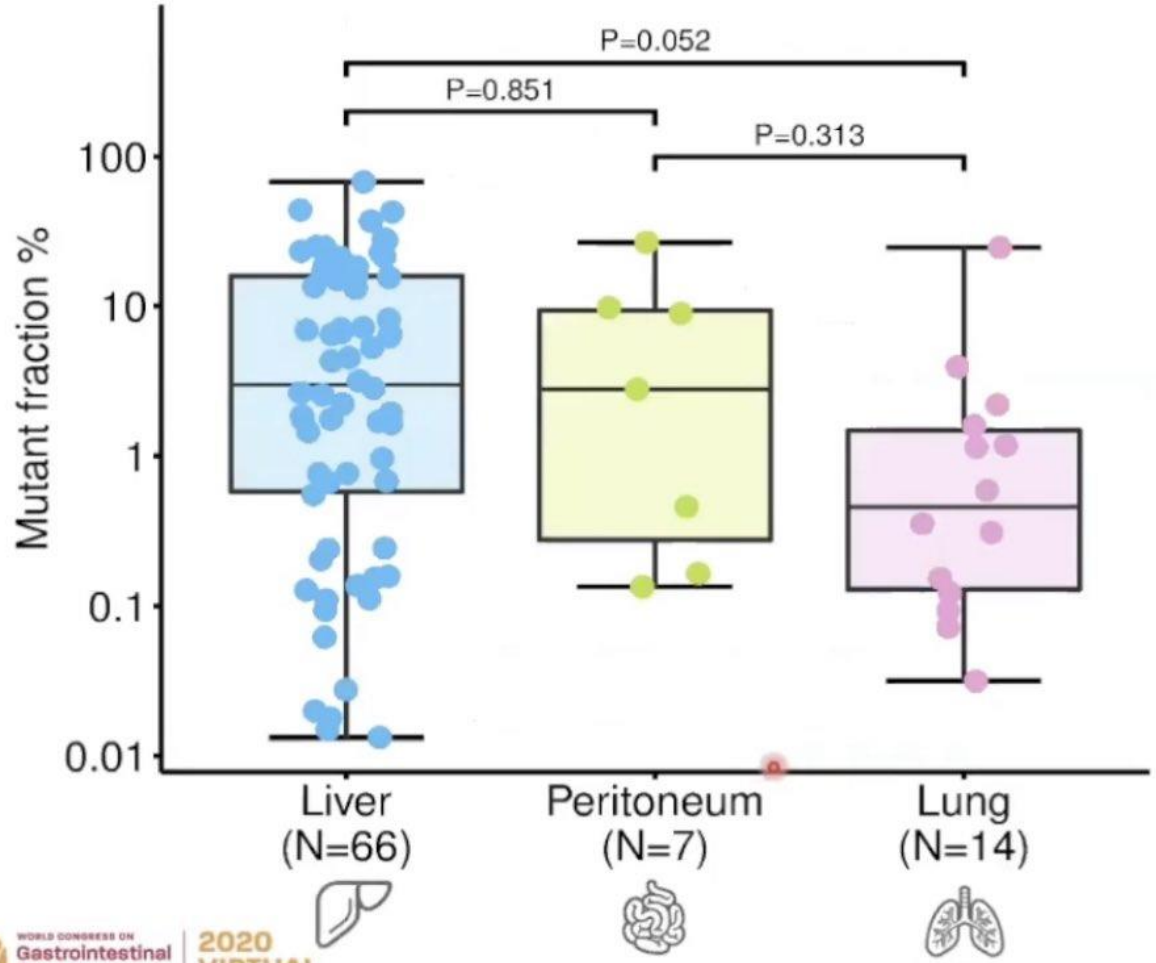
@pashtoonkasi

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

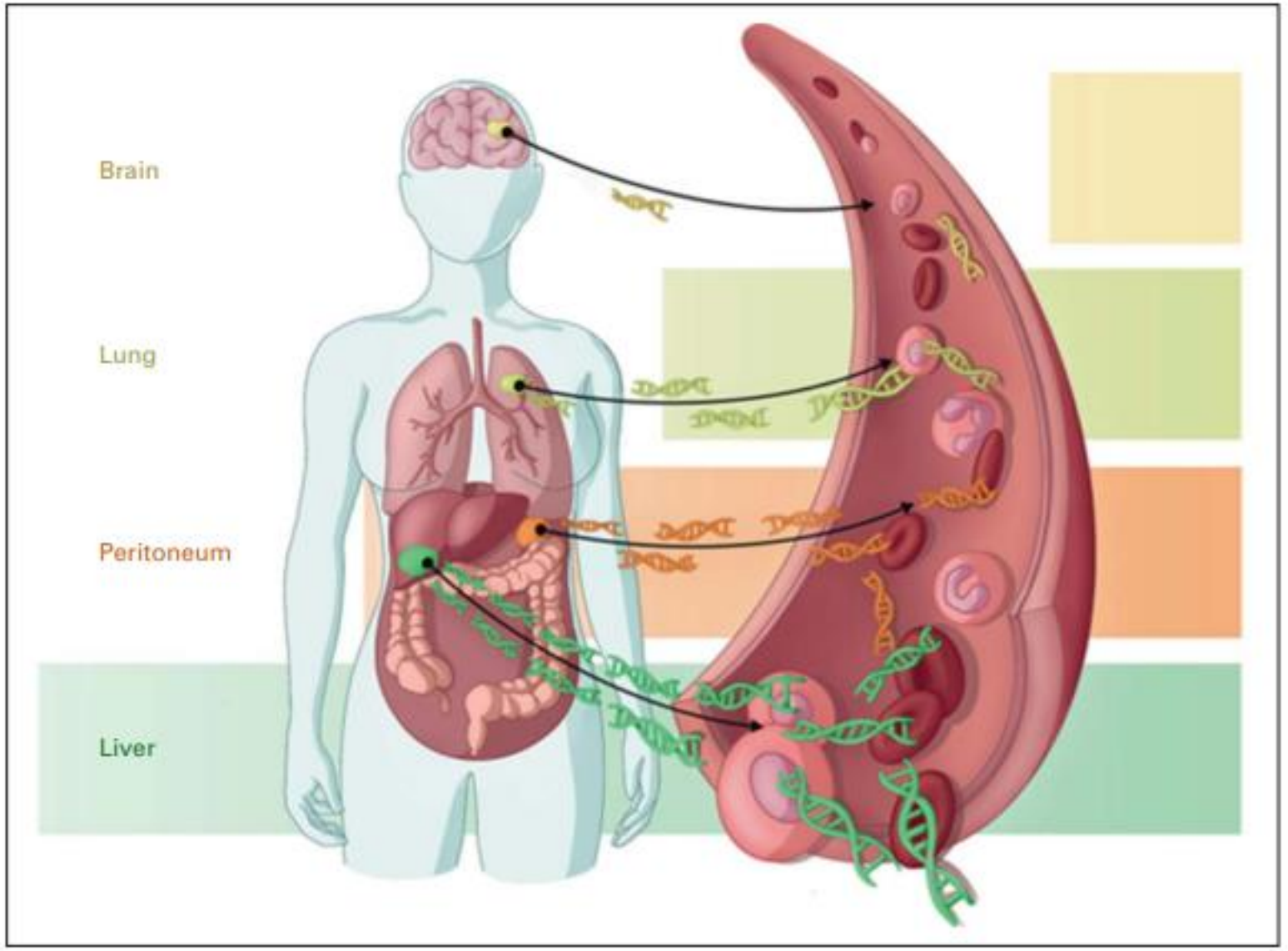
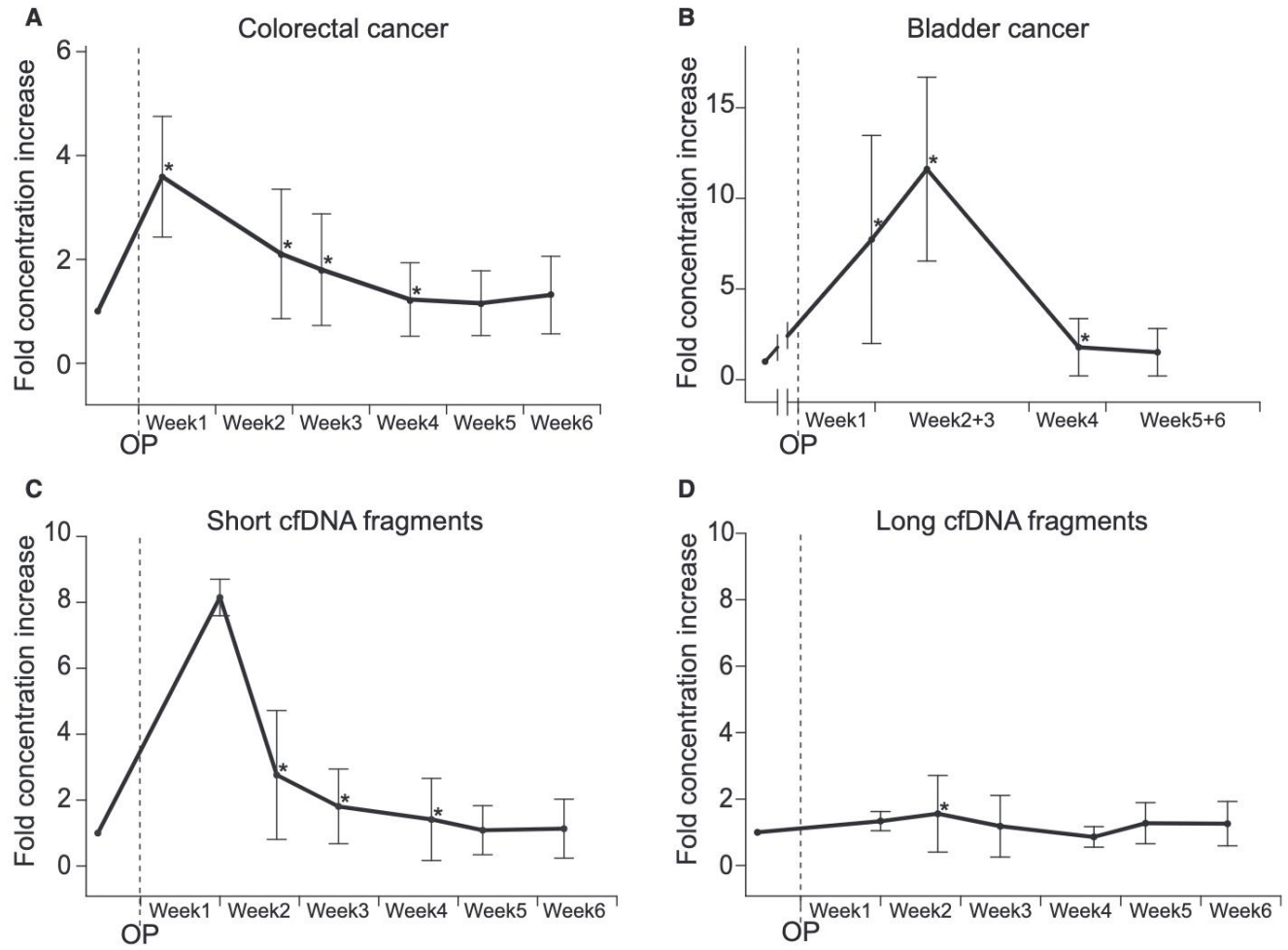


FIG 1. Shedding and amount of detectable circulating tumor DNA varies by location of metastatic site. Liver metastases appear to shed the most DNA, followed by the peritoneum and lung.

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.

Timing is key

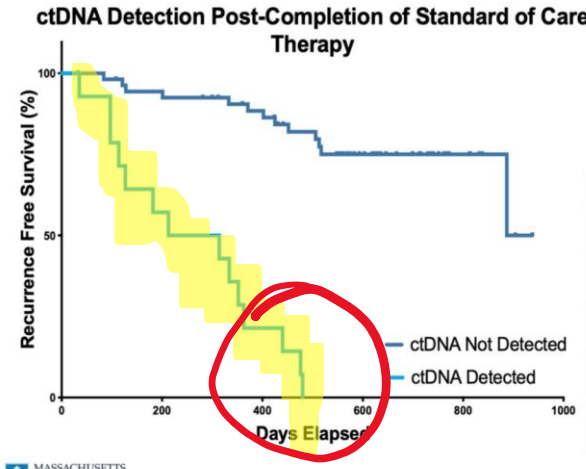
Finding the needle in the haystack

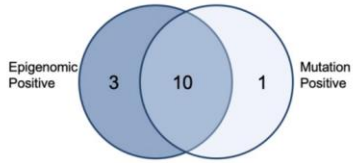
Immediate post-operative period – bigger haystack

Do ctDNA+ patients recur?

Does it correspond with outcomes (recurrence)?

Prediction of relapse post-SOC in CRC

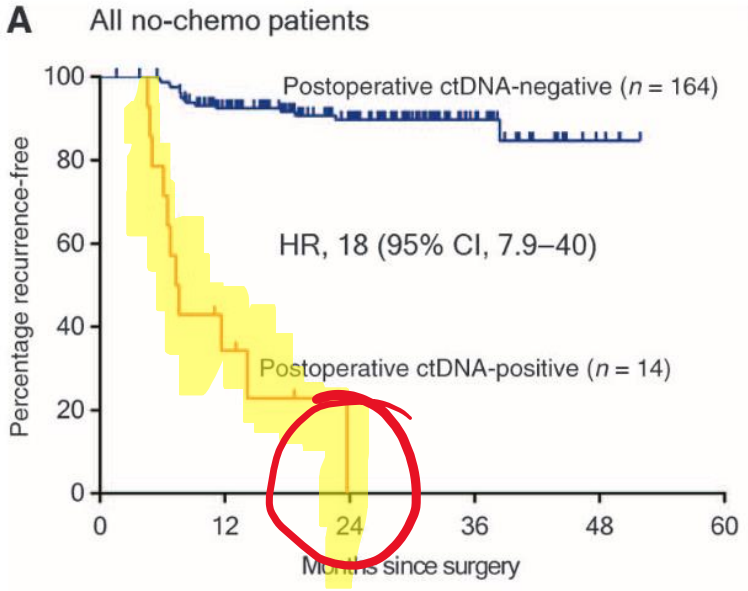




Assay Performance by Analysis		
	Genomic (N)	Integrated Genomic and Epigenomic (N)
PPV (N of patients with ctDNA detected who recurred)	100% (11 / 11)	100% (14 / 14)
NPV (N of patients with ctDNA not detected who were recurrence free)	72% (42 / 58)	76% (42 / 55)
Sensitivity for recurrence within one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

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

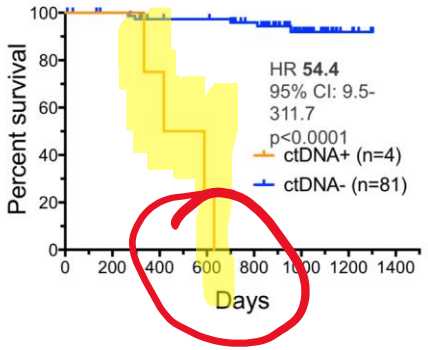
Parikh et al ASCO '19 #3602; Slide courtesy of Ryan Corcoran



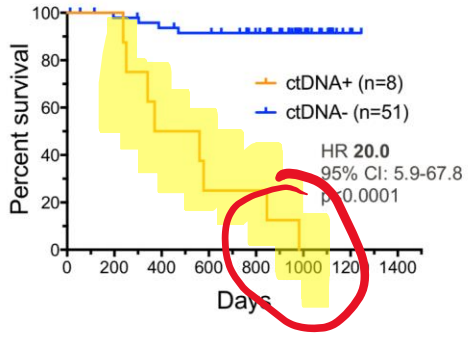
NGS Assay

Assay with 197 genes; at least one mutation detected 99.3% of tumor tissue
57% sensitivity for recurrence; 100% specificity

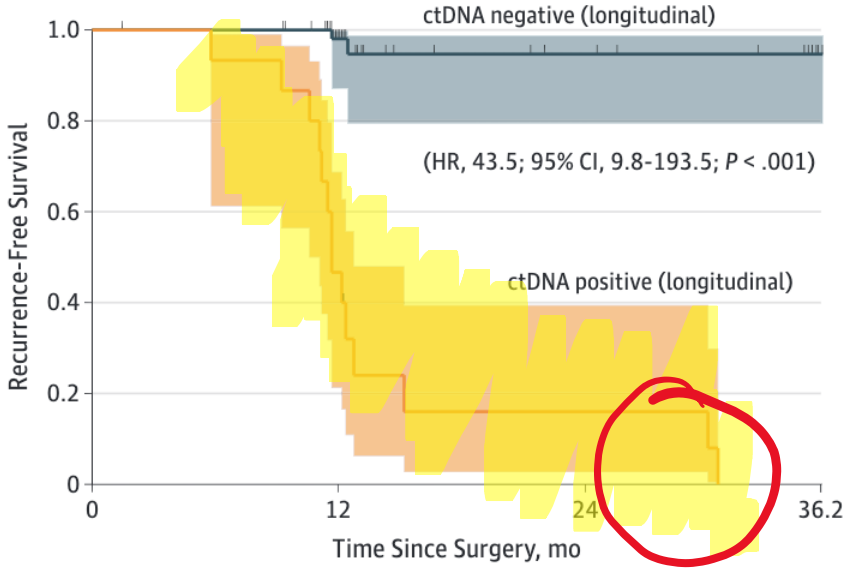
Stage II (5% prevalence of ctDNA+)



Stage III (16% prevalence of ctDNA+)



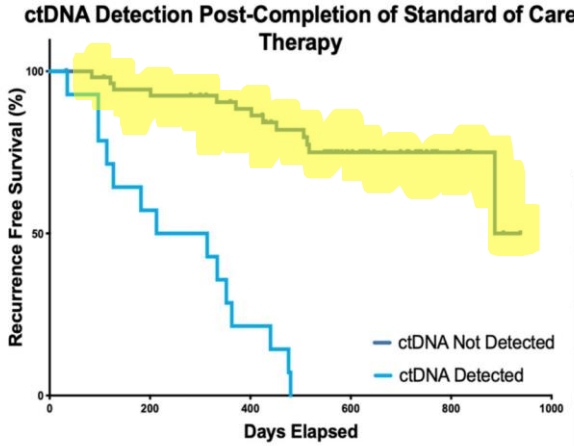
Diehn et al ASCO '17

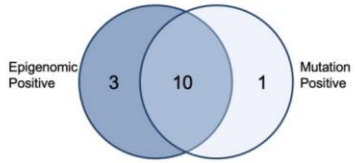


Do ctDNA- patients recur?

Does it correspond with outcomes (recurrence)?

Prediction of relapse post-SOC in CRC

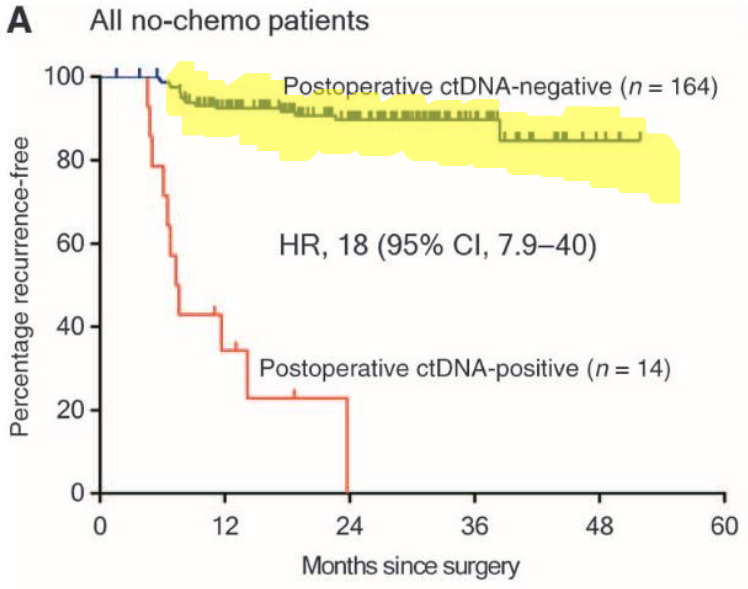




Assay Performance by Analysis		
	Genomic (N)	Integrated Genomic and Epigenomic (N)
PPV (N of patients with ctDNA detected who recurred)	100% (11 / 11)	100% (14 / 14)
NPV (N of patients with ctDNA not detected who were recurrence free)	72% (42 / 58)	76% (42 / 55)
Sensitivity for recurrence within one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

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

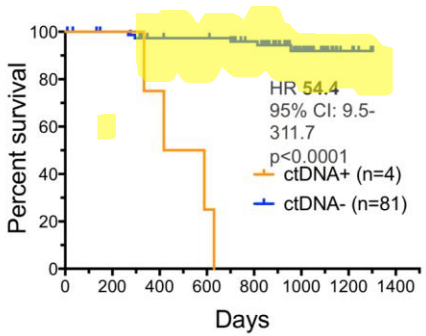
Parikh et al ASCO '19 #3602; Slide courtesy of Ryan Corcoran



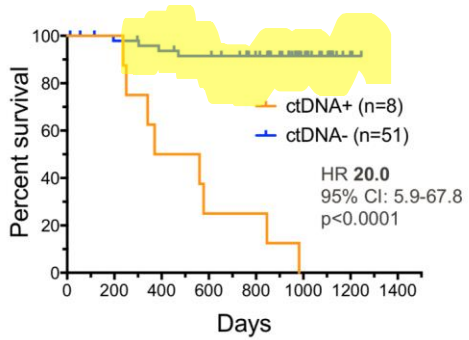
NGS Assay (Roche Molecular)

Assay with 197 genes; at least one mutation detected 99.3% of tumor tissue
57% sensitivity for recurrence; 100% specificity

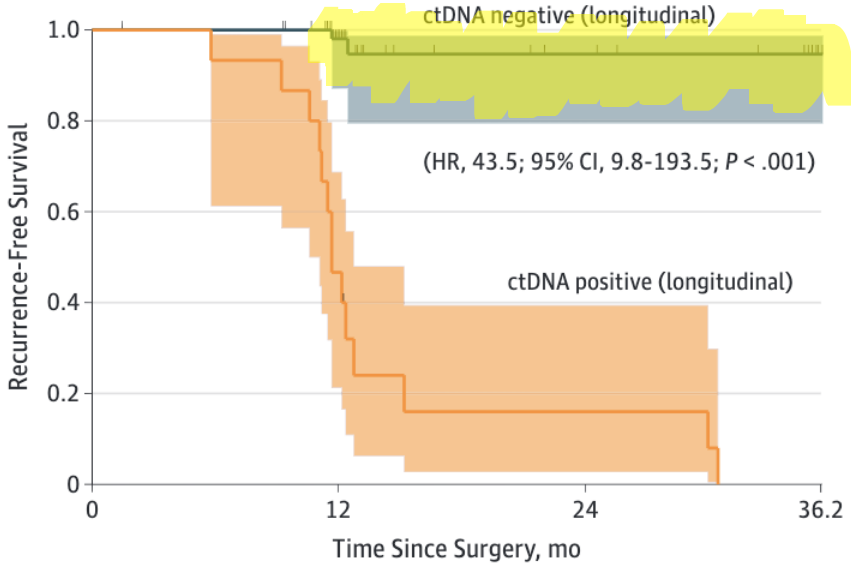
Stage II (5% prevalence of ctDNA+)



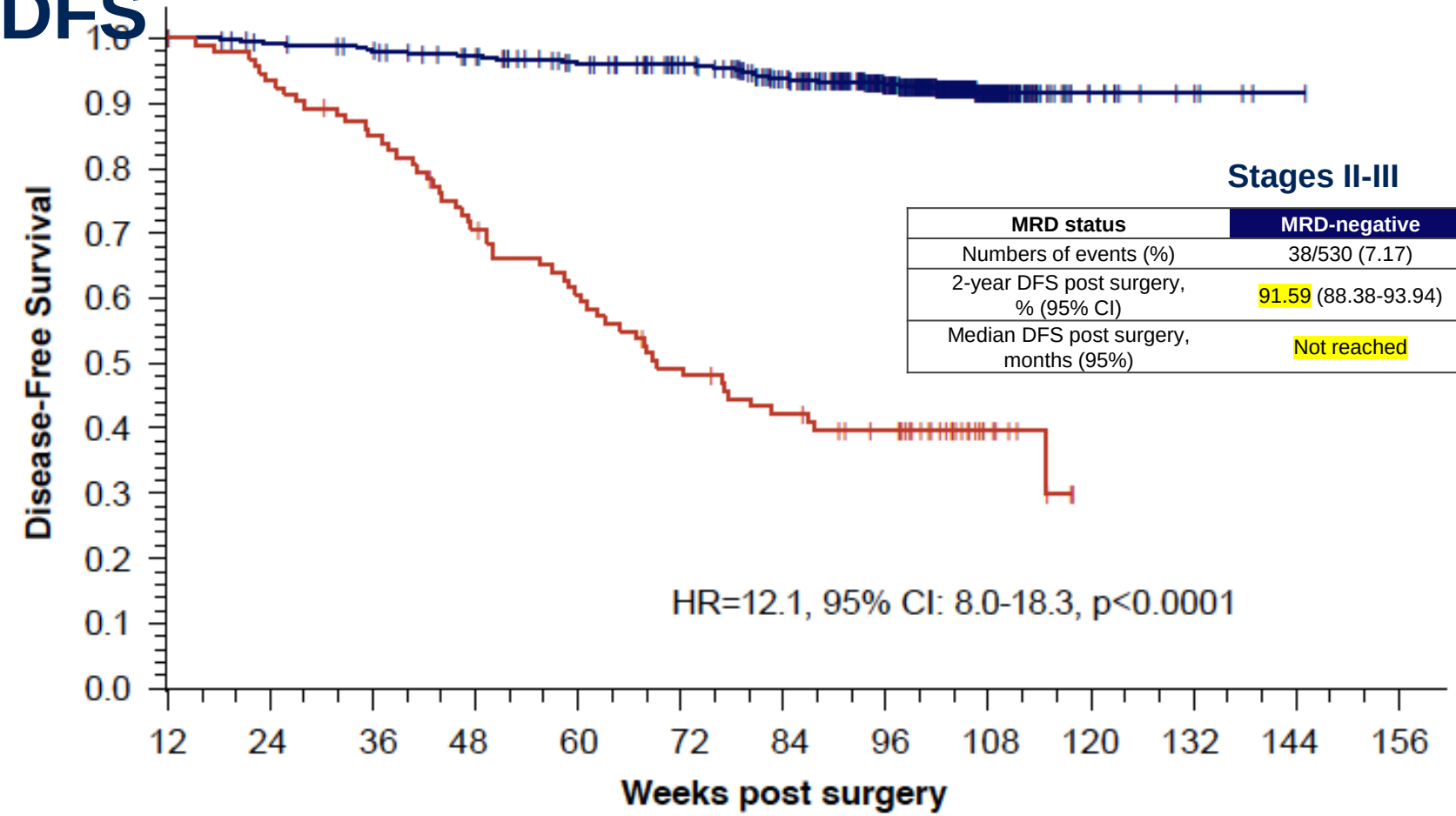
Stage III (16% prevalence of ctDNA+)



Diehn et al ASCO '17



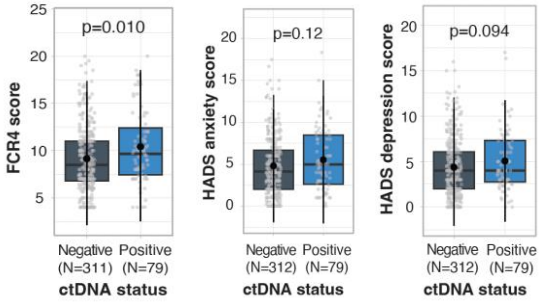
ctDNA-positivity at MRD time point is predictive of inferior DFS



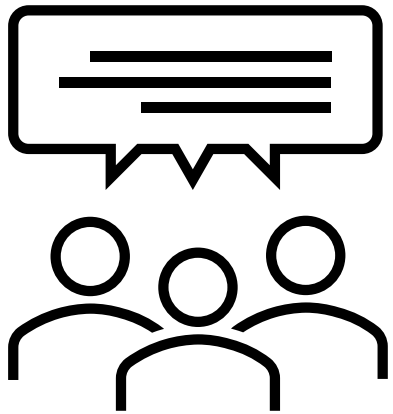
Stages II-III

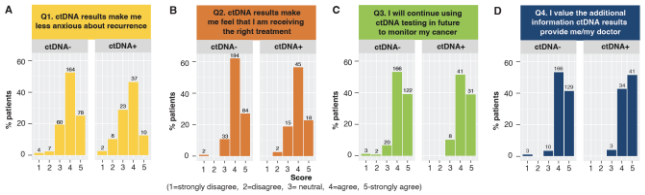
MRD status	MRD-negative	MRD-positive
Numbers of events (%)	38/530 (7.17)	55/93 (59.14)
2-year DFS post surgery, % (95% CI)	91.59 (88.38-93.94)	29.86 (13.26-48.54)
Median DFS post surgery, months (95%)	Not reached	15.98 (13.77-20.22)

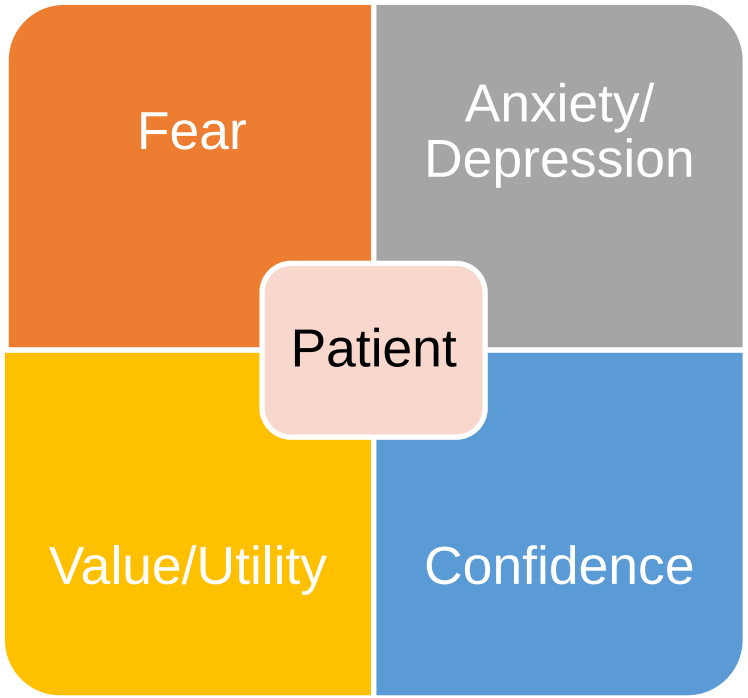
Perceived utility of ctDNA testing and dimensions of well-being



~1130 responses from 413 patients







73% reported ctDNA results reduced anxiety about cancer recurrence

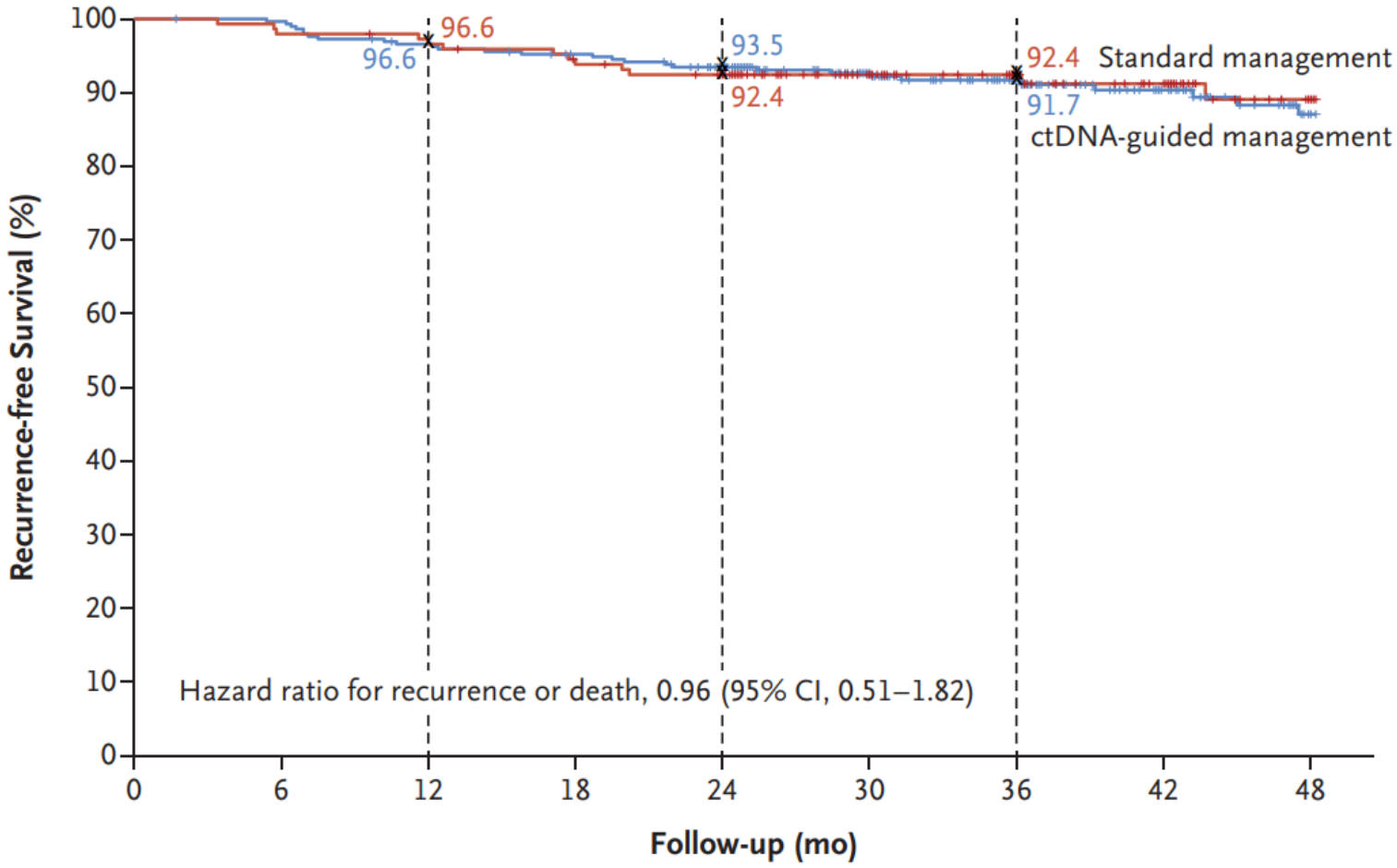
87% felt they were receiving the right treatment after receiving their results

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

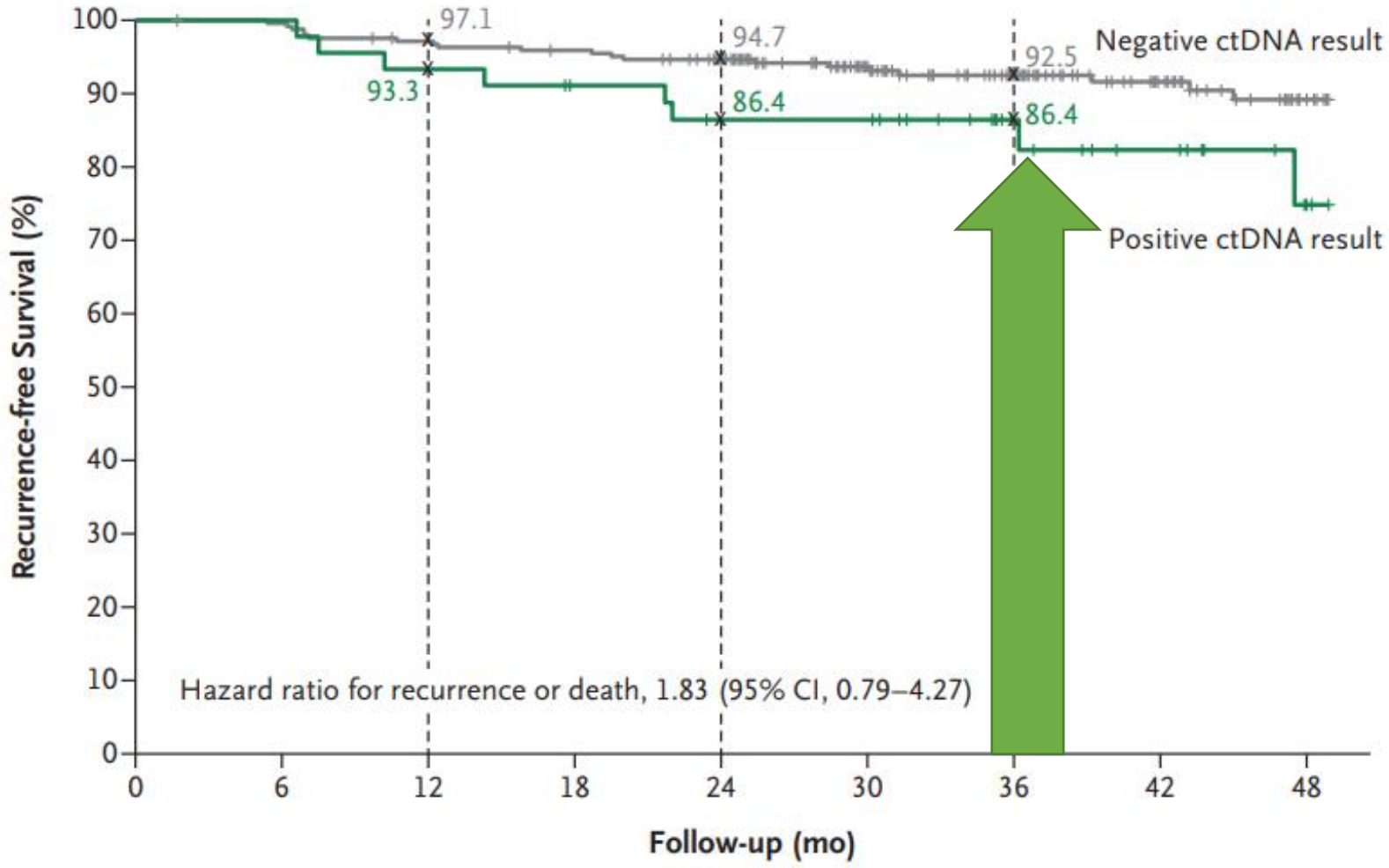
B Kaplan–Meier Estimates of Recurrence-free Survival



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 JOURNAL of MEDICINE

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

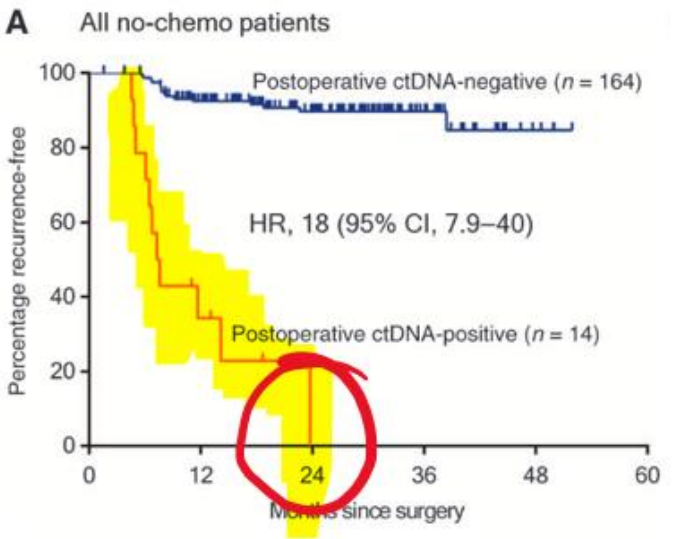


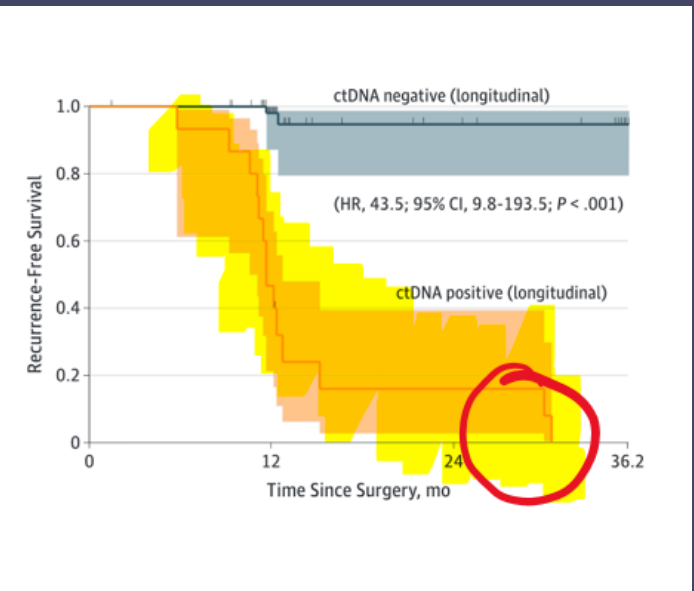
The NEW ENGLAND JOURNAL of MEDICINE

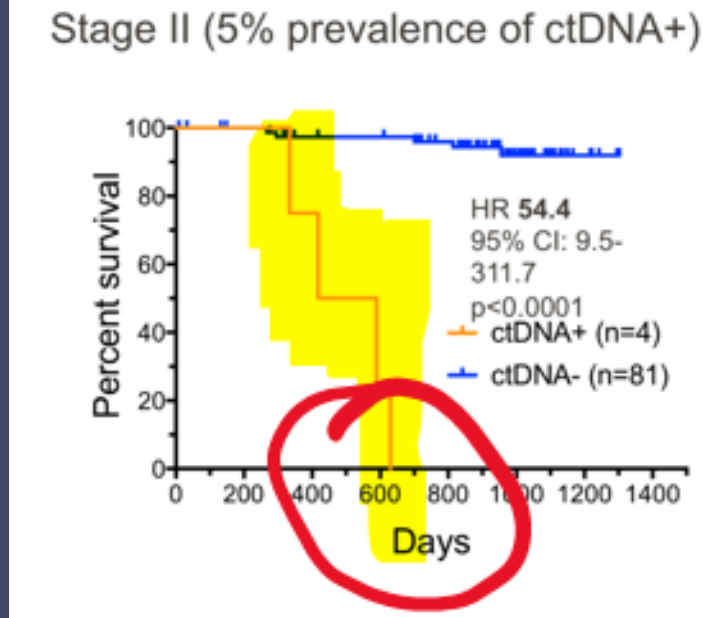
Tie et al. June 16, 2022
N Engl J Med 2022; 386:2261-2272

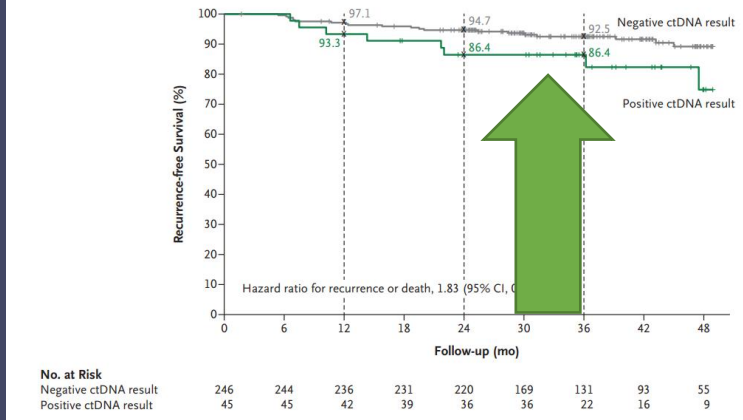
No. at Risk

Negative ctDNA result	246	244	236	231	220	169	131	93	55
Positive ctDNA result	45	45	42	39	36	36	22	16	9



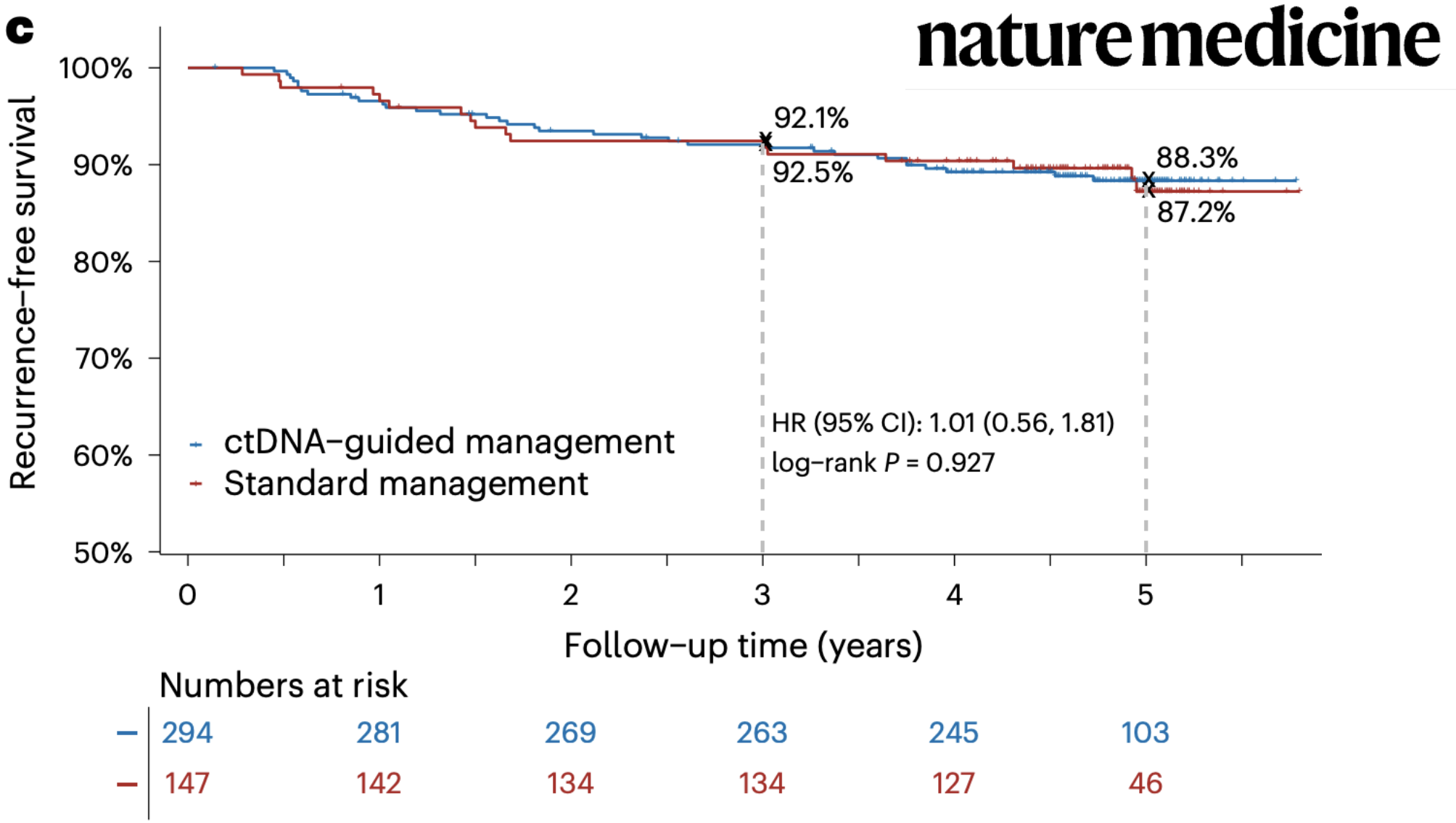






The NEW ENGLAND JOURNAL of MEDICINE

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


c
nature medicine
Recurrence–free survival
100%
90%
80%
70%
60%
50%
92.1%
92.5%
88.3%
87.2%
ctDNA–guided management
Standard management
HR (95% CI): 1.01 (0.56, 1.81)
log–rank P = 0.927
0
1
2
3
4
5
Follow–up time (years)
Numbers at risk
294 281 269 263 245 103
147 142 134 134 127 46

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

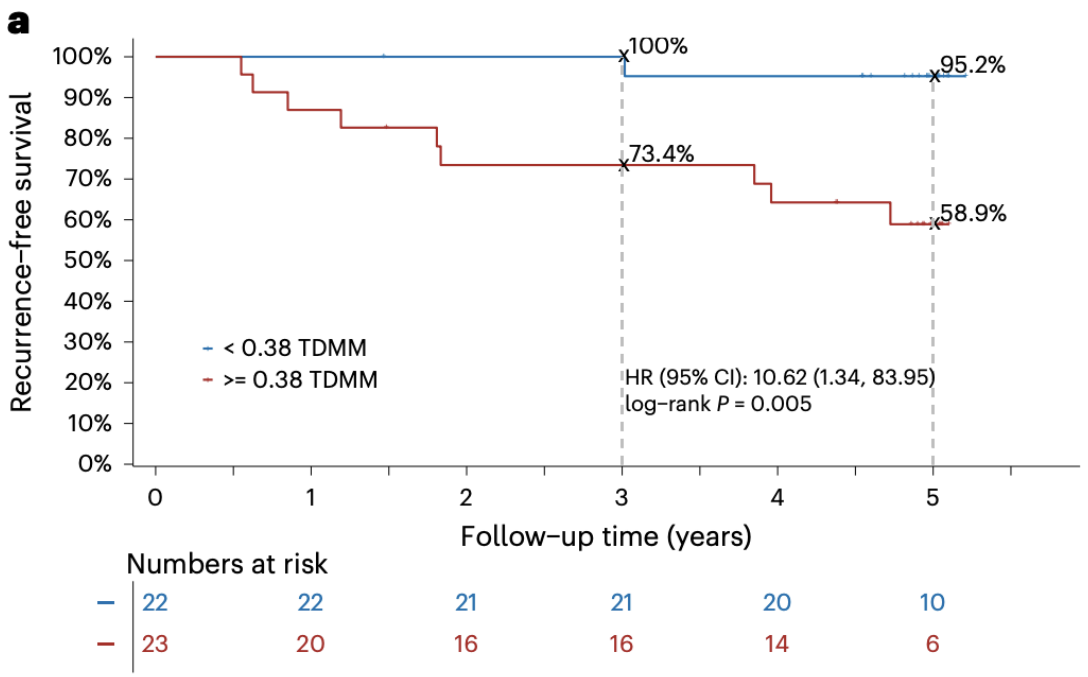
- Parts per million

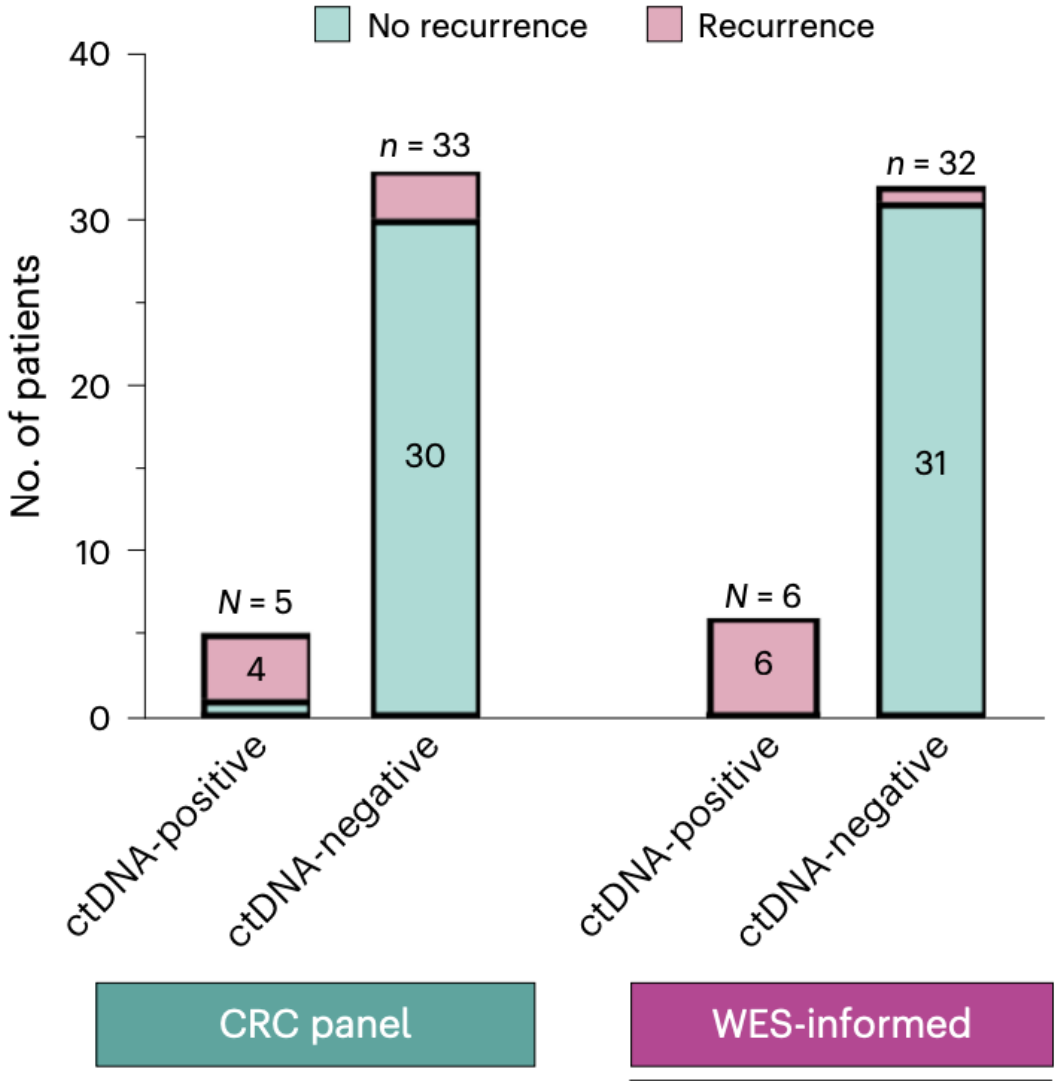
Relative measurement

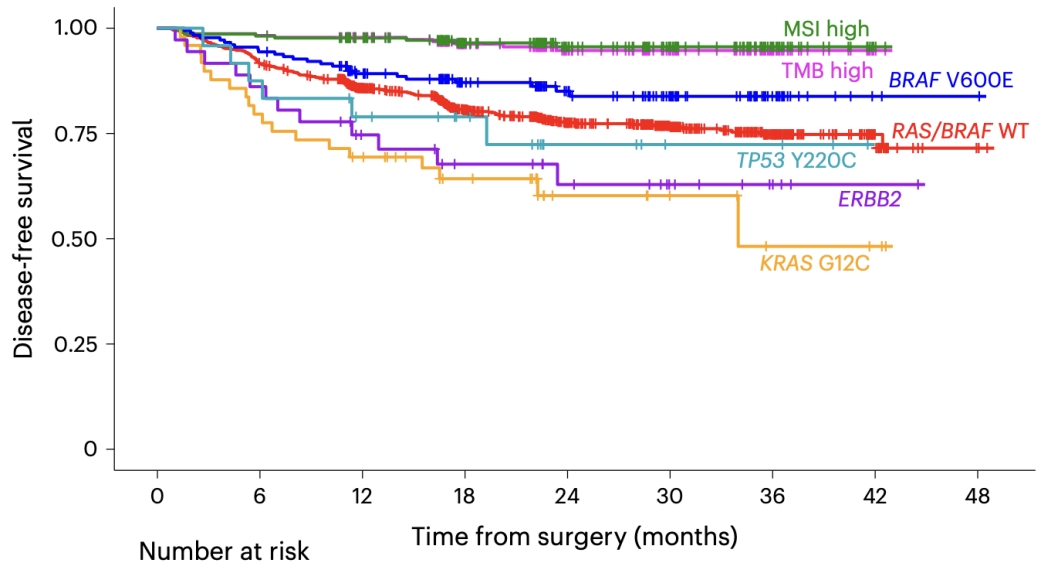
Focuses on the ratio of ctDNA molecules containing MRD targets out of the total cfDNA molecules measured (ctDNA + normal cfDNA)

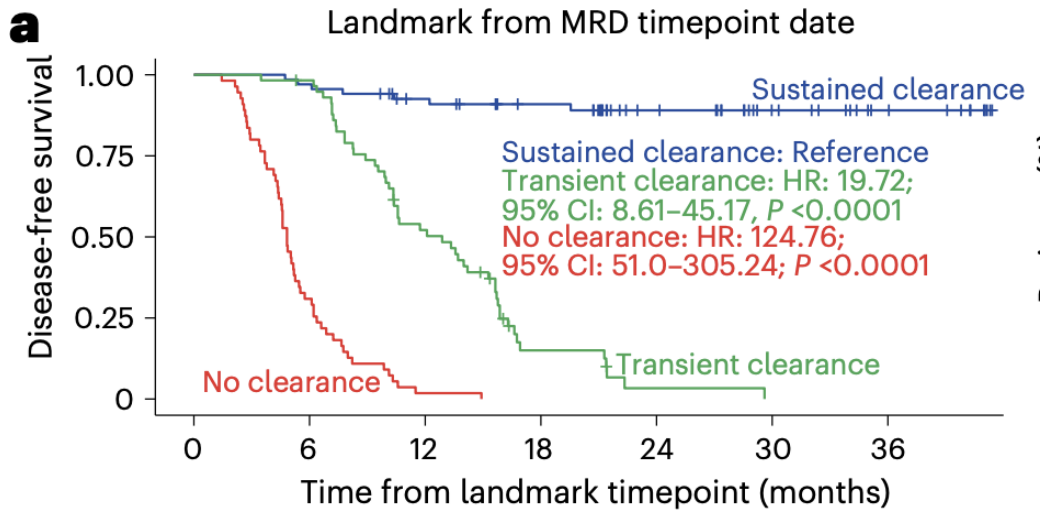
1.67 parts per million (PPM) = 1.67×10^{-6} tumor fraction = 0.000167% VAF

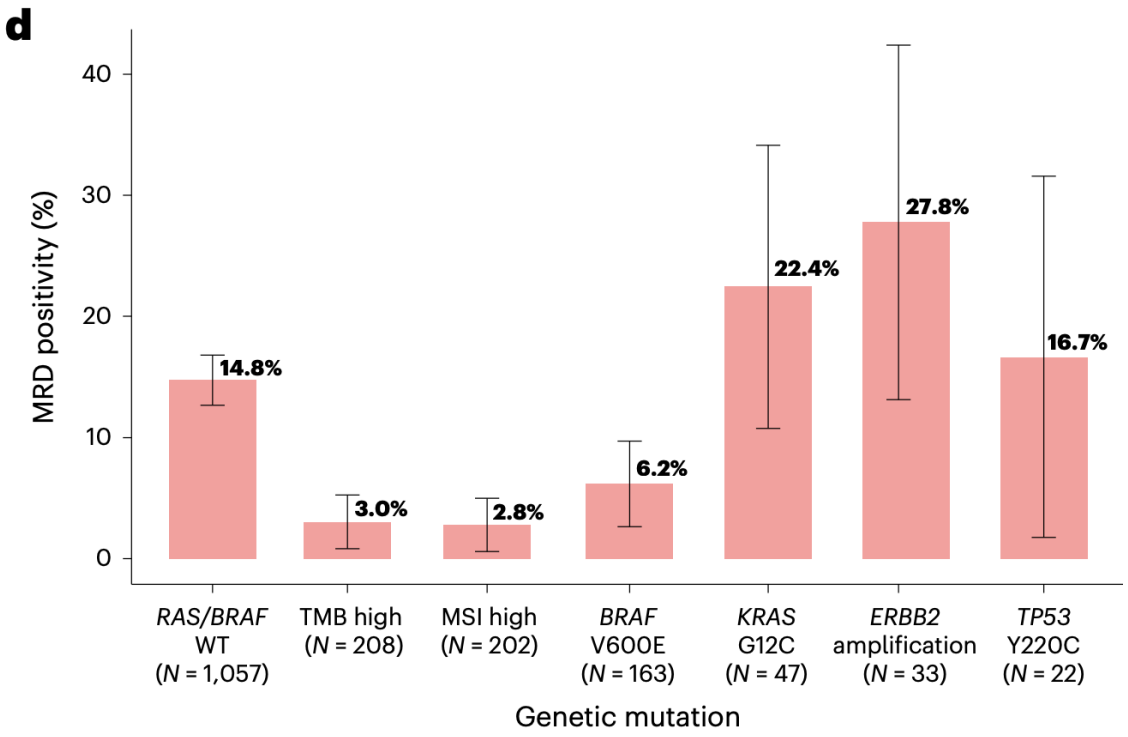
nature medicine






1.00
0.75
0.50
0.25
0
Disease-free survival
MSI high
TMB high
BRAF V600E
RAS/BRAF WT
TP53 Y220C
ERBB2
KRAS G12C
0
6
12
18
24
30
36
42
48
Number at risk
Time from surgery (months)


a
Landmark from MRD timepoint date
1.00
0.75
0.50
0.25
0
Disease-free survival
Sustained clearance
Sustained clearance: Reference
Transient clearance: HR: 19.72;
95% CI: 8.61–45.17, P <0.0001
No clearance: HR: 124.76;
95% CI: 51.0–305.24; P <0.0001
Transient clearance
No clearance
0
6
12
18
24
30
36
Time from landmark timepoint (months)


d
40
30
20
10
0
MRD positivity (%)
14.8%
3.0%
2.8%
6.2%
22.4%
27.8%
16.7%
RAS/BRAF WT (N = 1,057)
TMB high (N = 208)
MSI high (N = 202)
BRAF V600E (N = 163)
KRAS G12C (N = 47)
ERBB2 amplification (N = 33)
TP53 Y220C (N = 22)
Genetic mutation

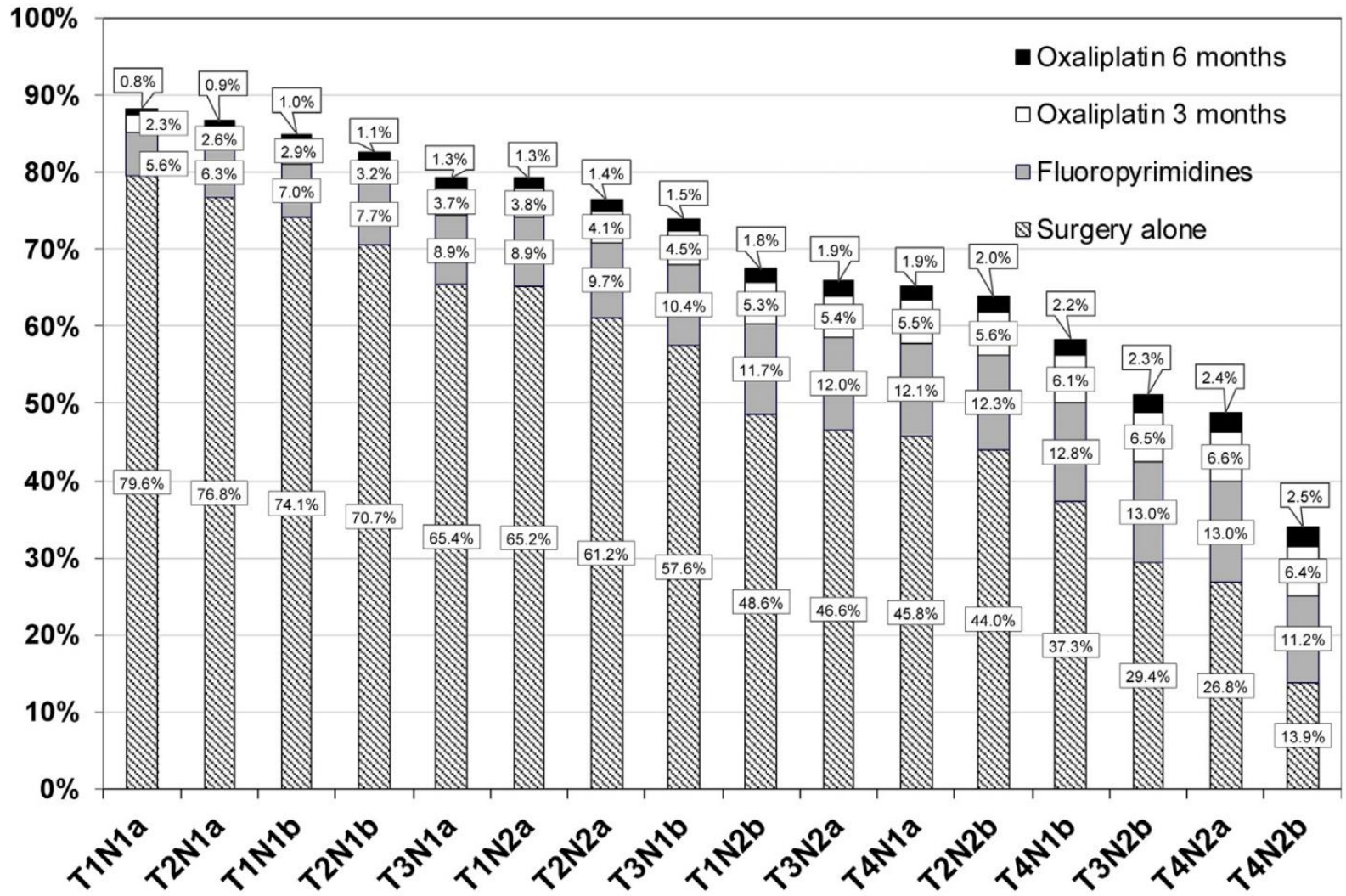
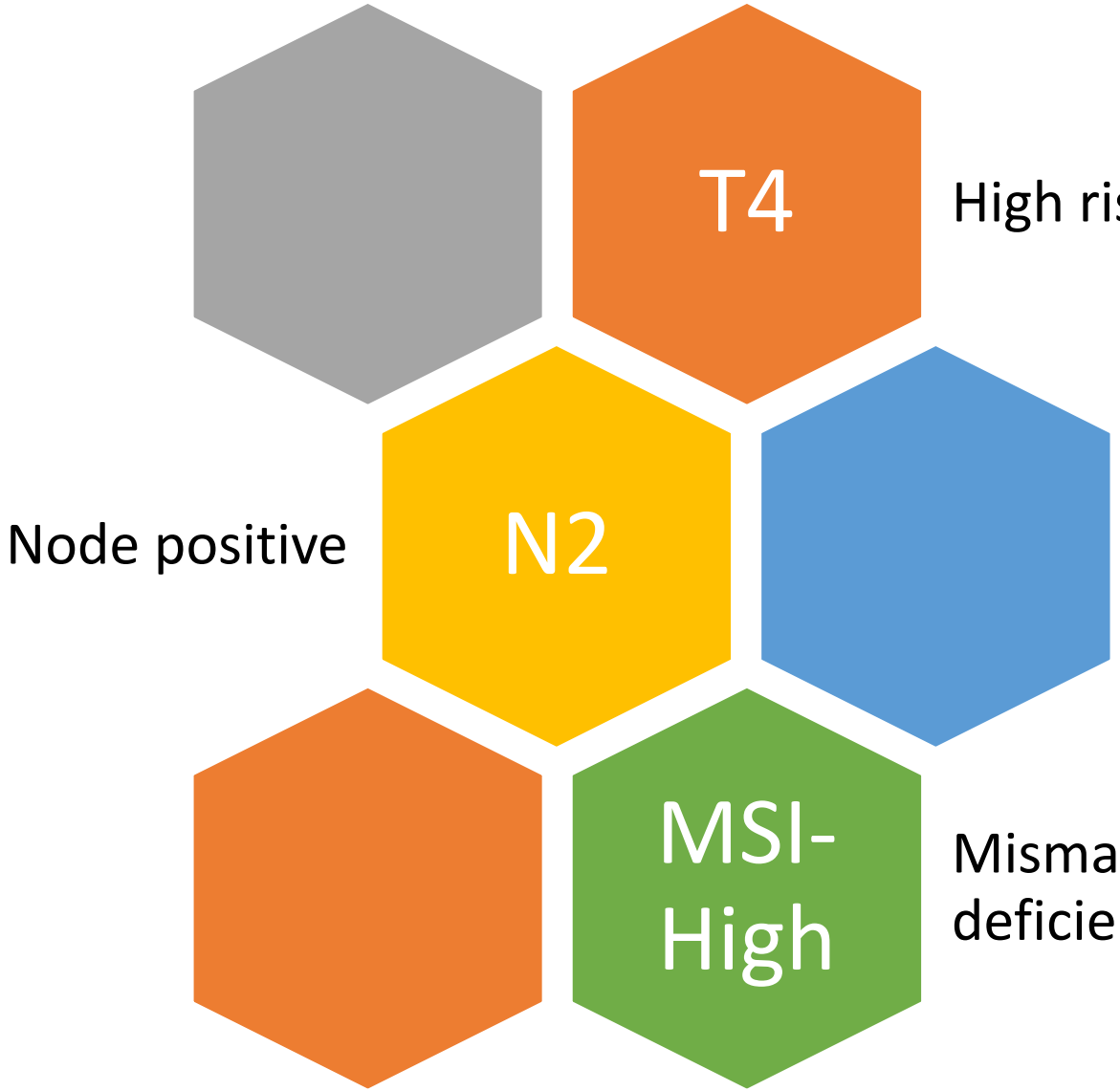


Fig. 2. Predicted 5-year DFS in the 16 prognostic sub-stages within stage III treated with surgery alone (dashed bar, HR = 0.7); fluoropyrimidine alone (light grey bar, HR = 0.78); oxaliplatin-based doublet for 3 months (white bar, HR = 0.93), oxaliplatin-based doublet for 6 months (black bar).

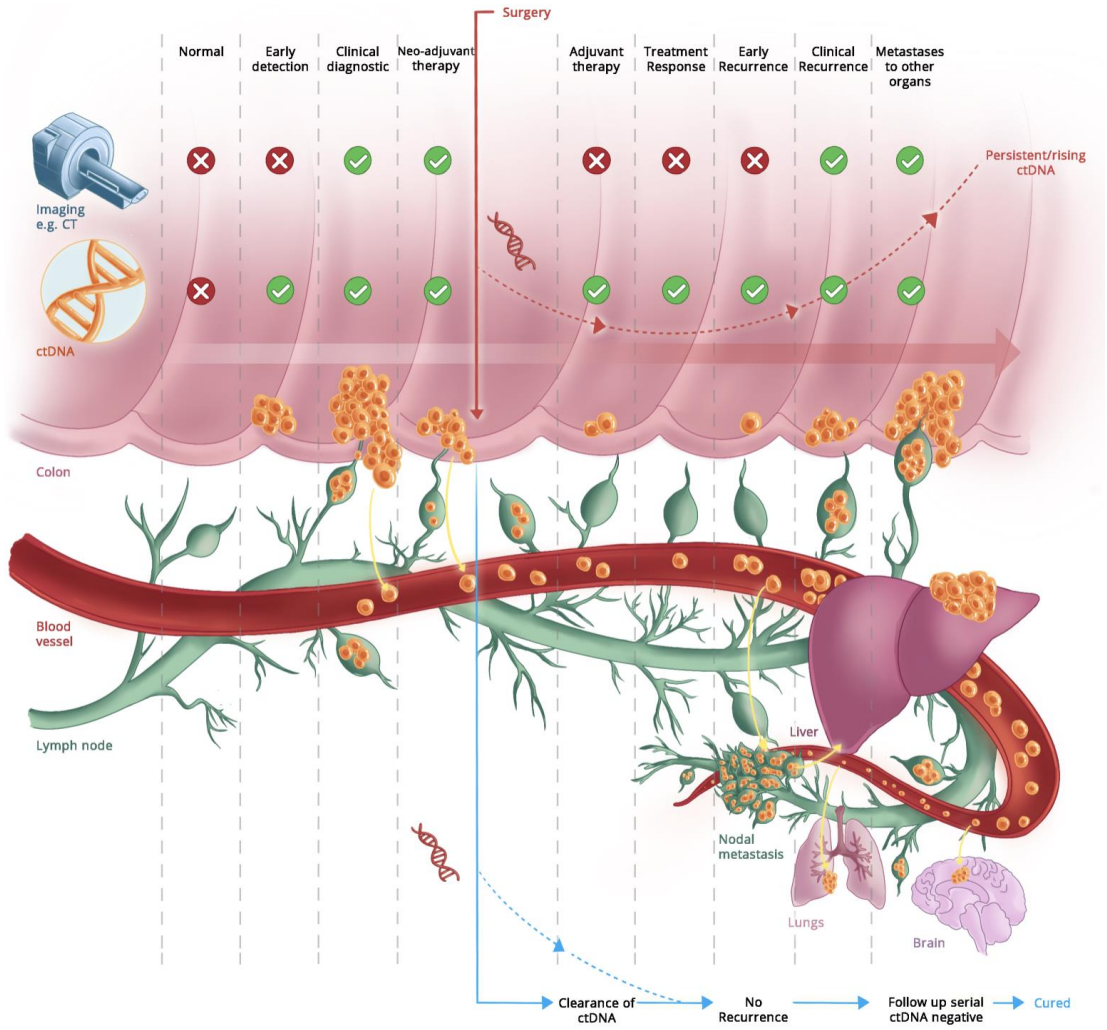


Summary/Future Directions

CtDNA

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

@pashtoonkasi[7]

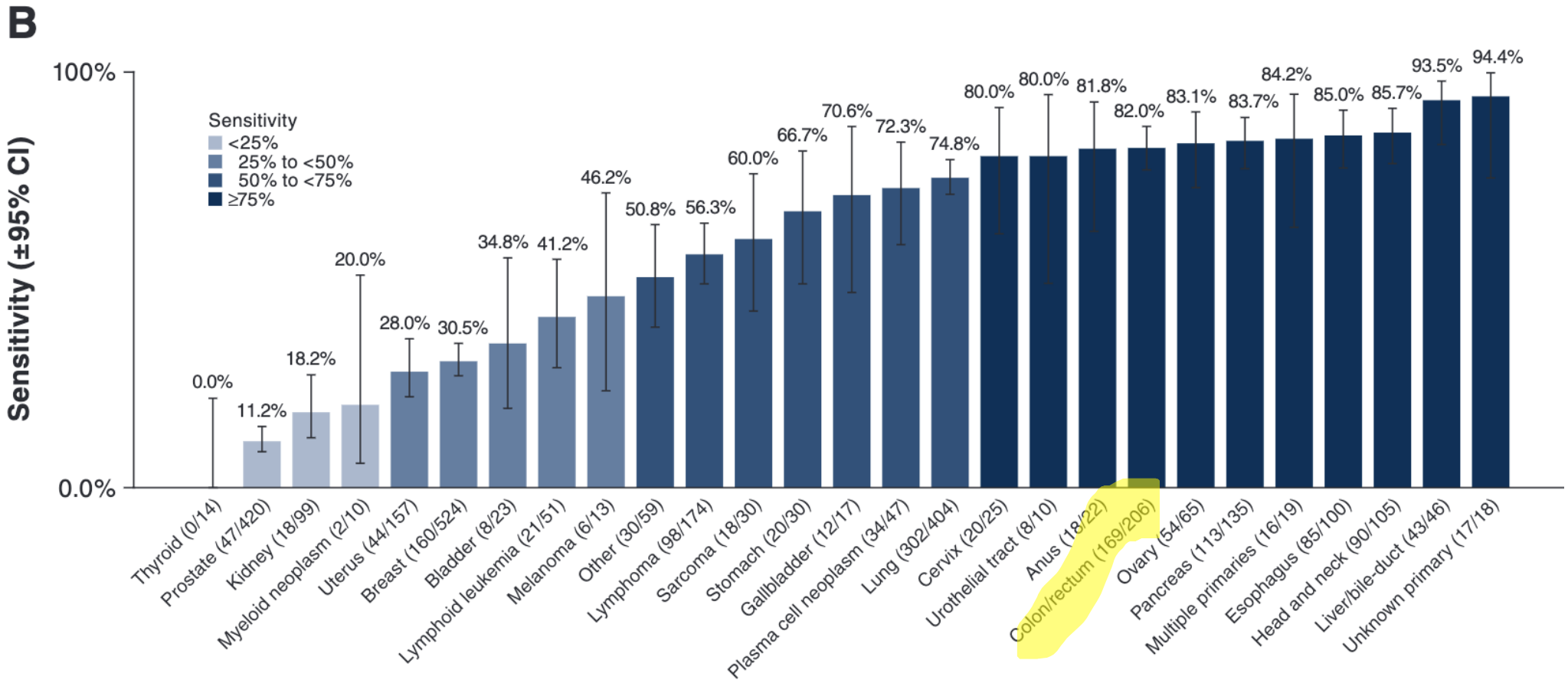


Tumor DNA-Based Screening Approaches for Colorectal Cancer

1. Colorectal Cancer specific tests

2. Multi-tumor agnostic tests

Targeted methylation-based multi-cancer early detection test (MCED)



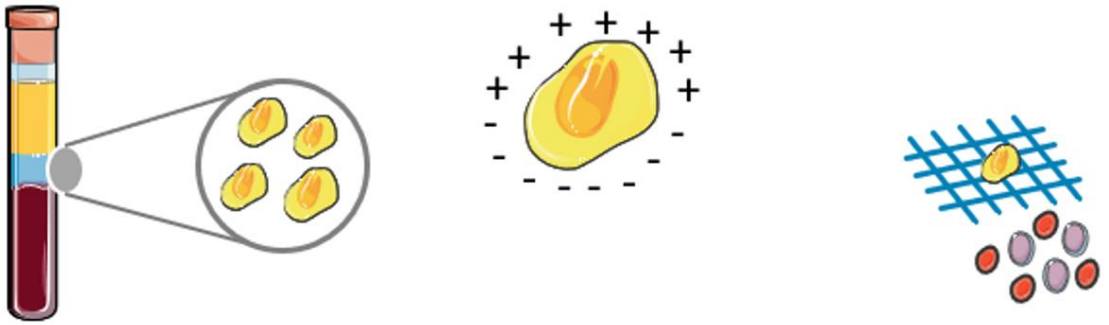
Klein EA, et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. ***Annals of Oncology 2021****;32(9):1167-77*

Circulating Tumor Cells

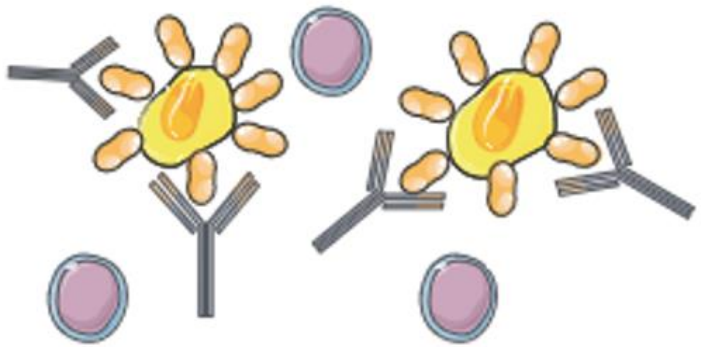
CTCs

CTC Isolation Techniques

Surface independent approaches



Surface dependent approaches

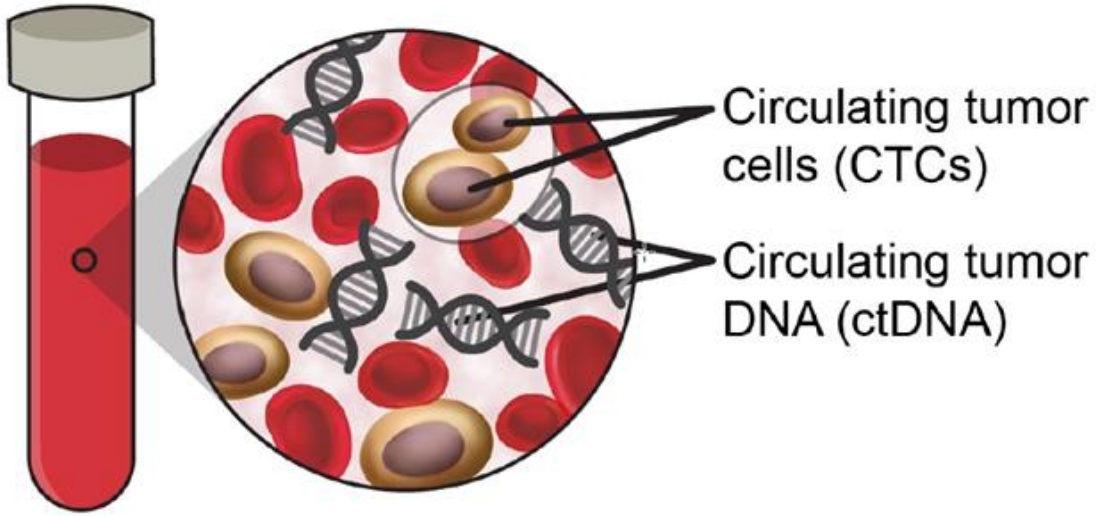


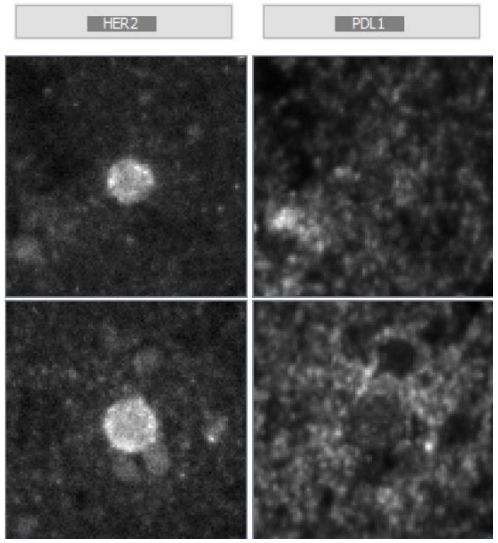
Peripheral Blood Cell

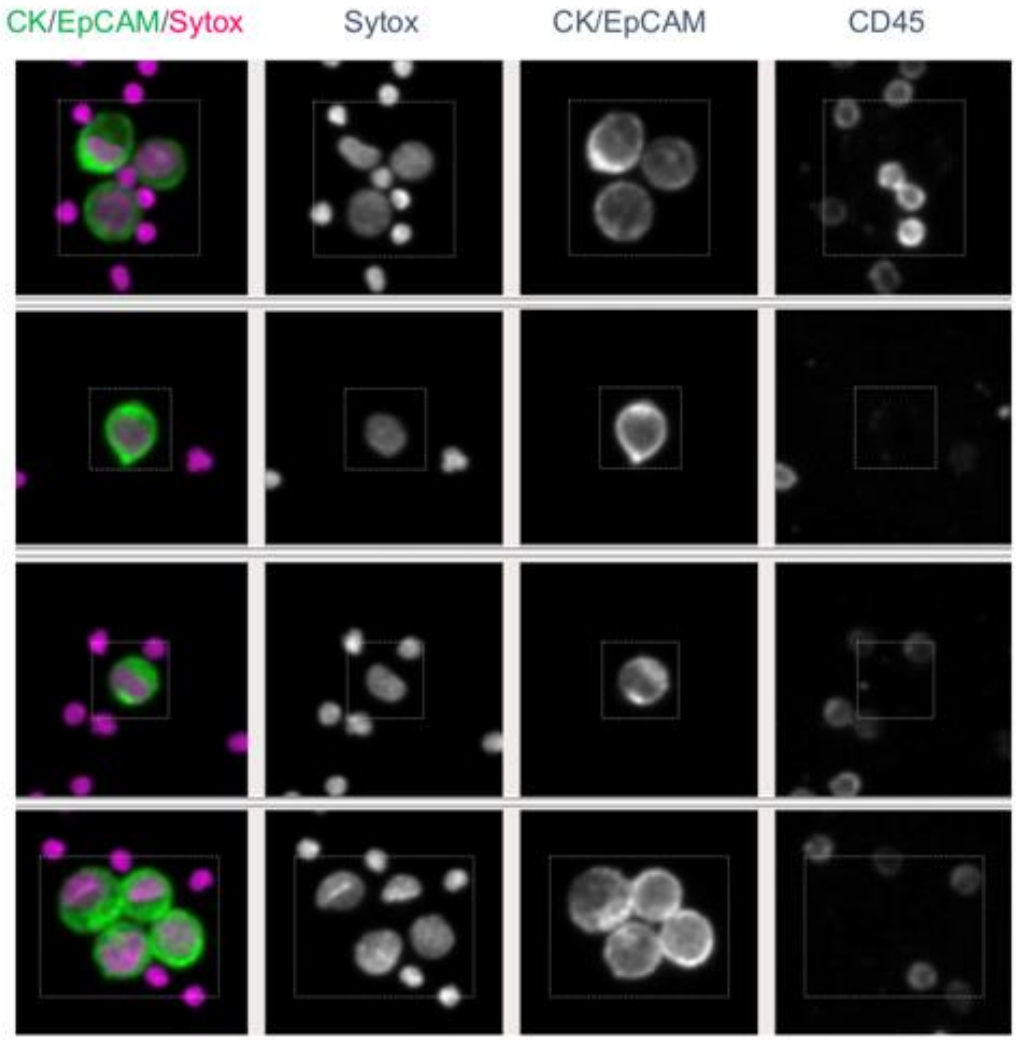
CTC

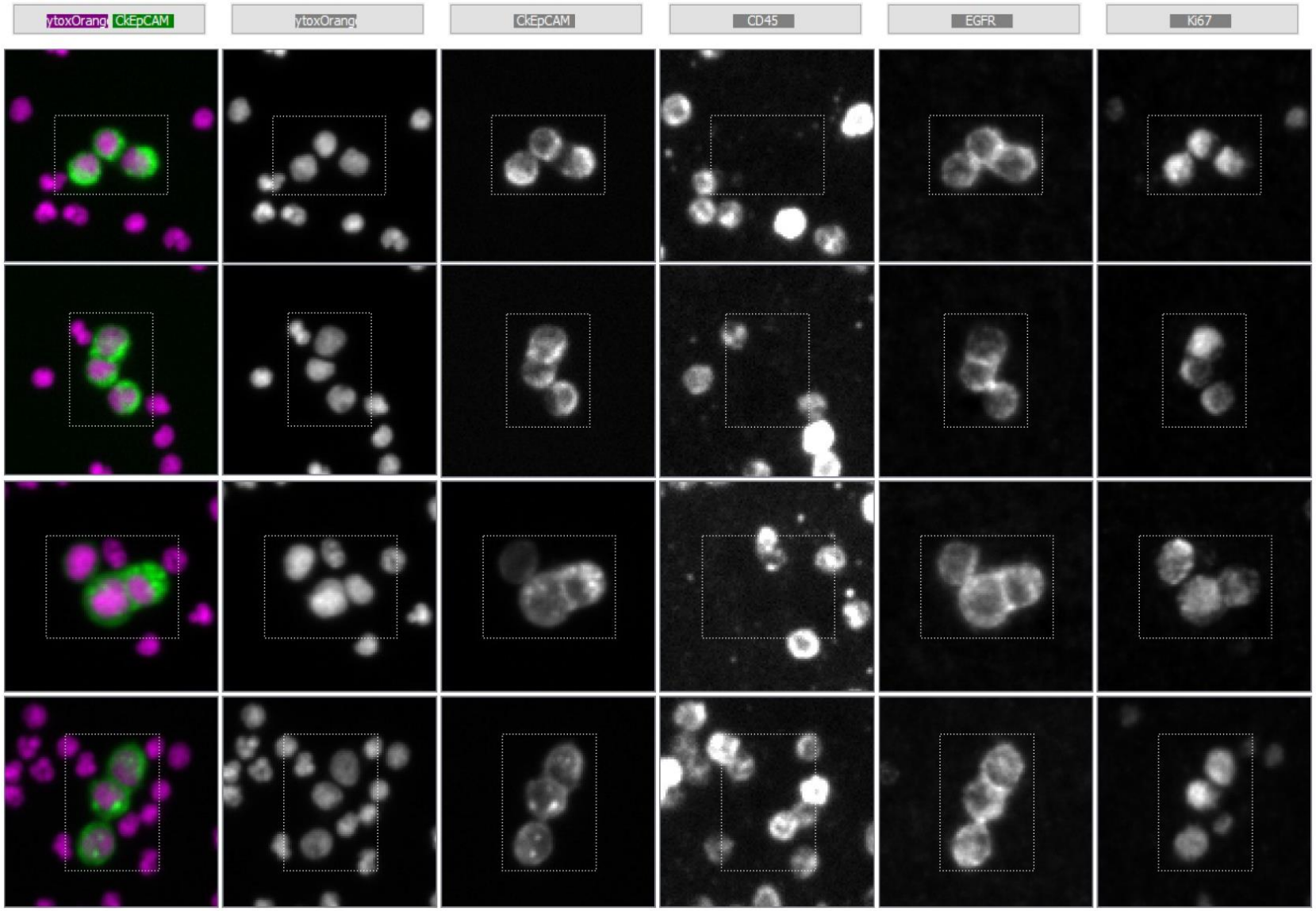
EPCAM

Anti-EPCAM Antibody


Circulating tumor cells (CTCs)
Circulating tumor DNA (ctDNA)


HER2
PDL1


CK/EpCAM/Sytox
Sytox
CK/EpCAM
CD45



Biomarkers

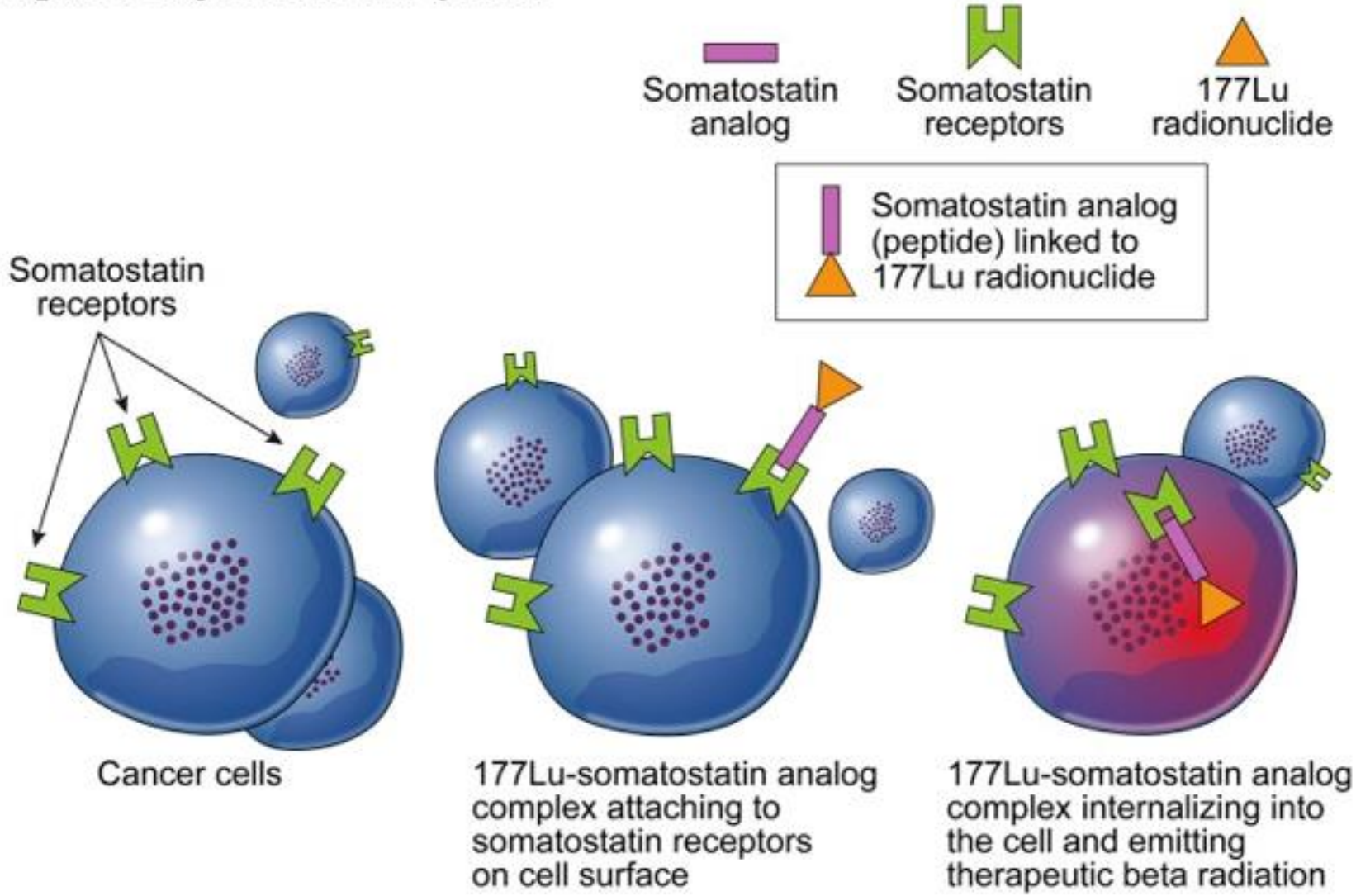
EGFR

Ki67

HER2

PD-L1

***Figure 4**: Simplistic overview of PRRT*



Pashtoon Kasi, MD, MS

City of Hope.
kasi@coh.org
Cell: 412-897-2301

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

doi: 10.1200/JCO.21.02615.
PMID: 35839443.

SPECIAL SERIES: PRECISION MEDICINE AND IMMUNOTHERAPY IN GI MALIGNANCIES

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

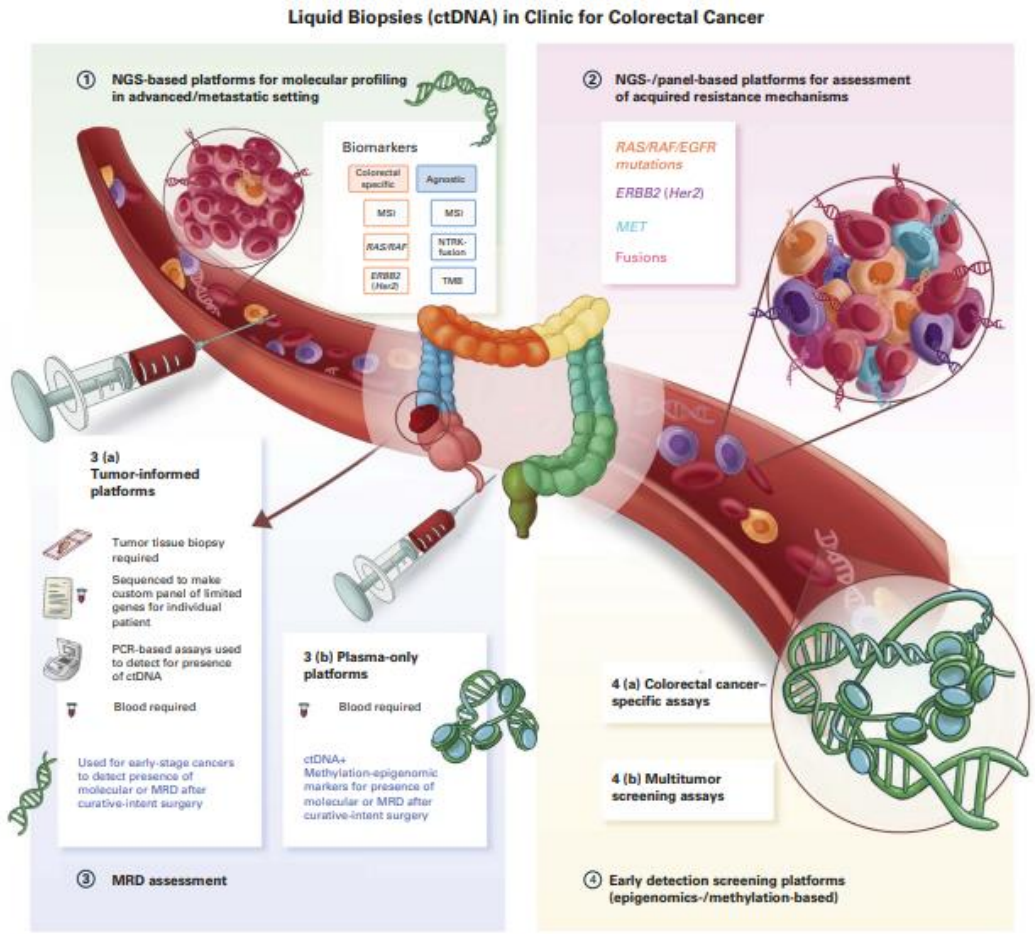
Midhun Malla, MD, MS[1]; Jonathan M. Loree, MD, MS[2]; Pashtoon Murtaza Kasi, MD, MS[3]; and Aparna Raj Parikh, MD[4]

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



ctDNA's Role in Shaping the Present and Future of GI Cancer Treatment

Pashtoon Kasi, MD, MS

Medical Director of GI Oncology,
City of Hope Orange County.
Rad Family Chair in Gastrointestinal Oncology
kasi@coh.org
X: @pashtoonkasi