How I Use Liquid Biopsy for GI Cancers in 2023

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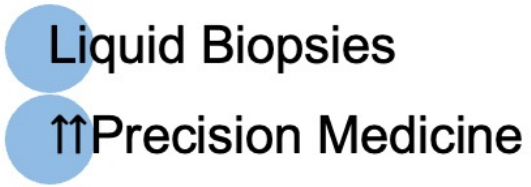
NewYork-Presbyterian

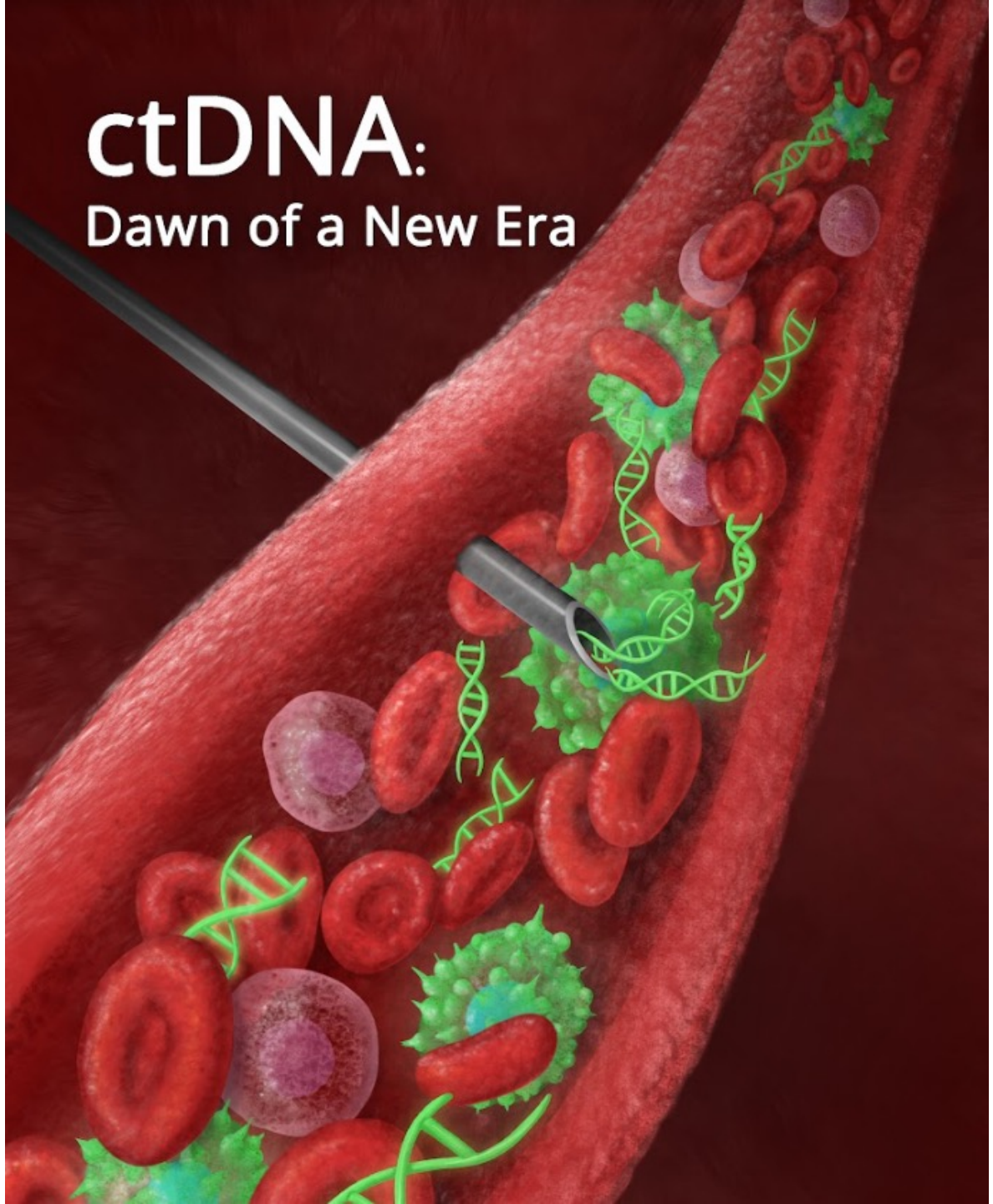
Englander Institute
for Precision Medicine

Sandra and Edward
Meyer Cancer Center

Key Learning Objectives

1. Understand how liquid biopsies are increasing **opportunities** for precision medicine in cancer care
2. Understand the different **types of liquid biopsies**, and their associated optimal use
3. Liquid biopsies for detecting **minimal residual disease (MRD)**, and **screening**



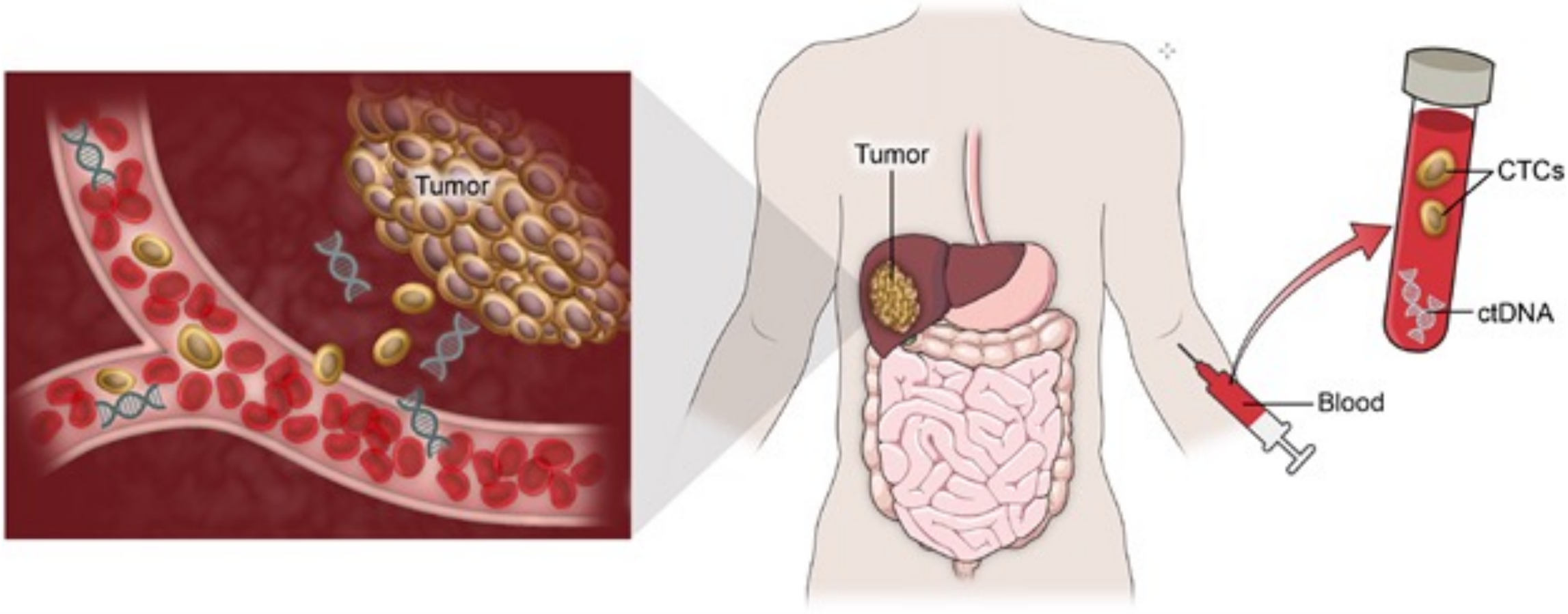


ctDNA: Dawn of a New Era

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



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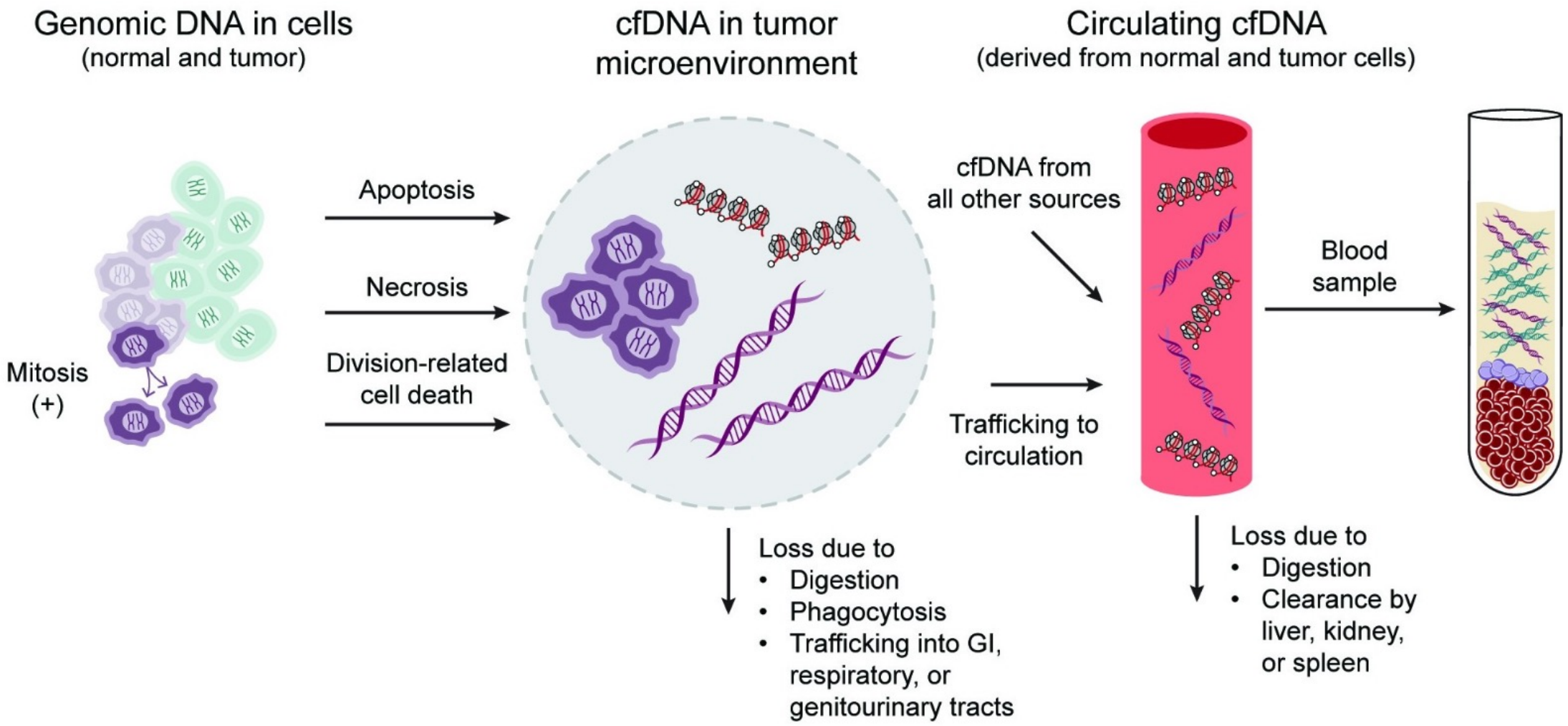
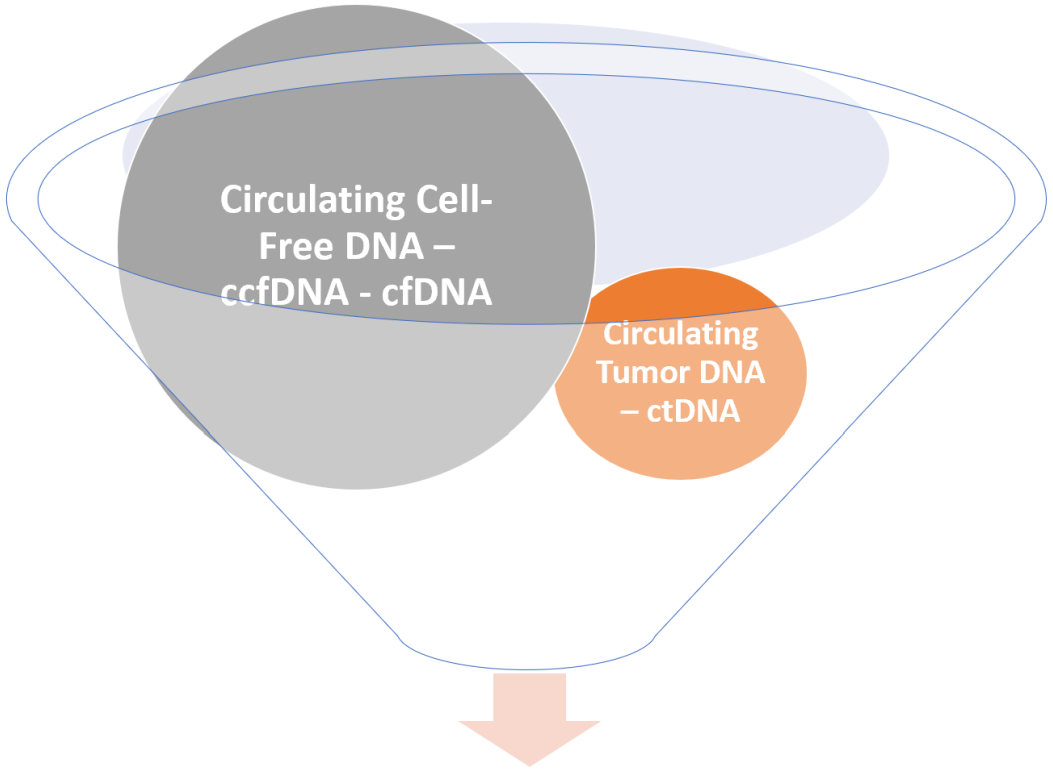
Depiction of origin and fates of circulating tumor DNA relative to cell-free DNA

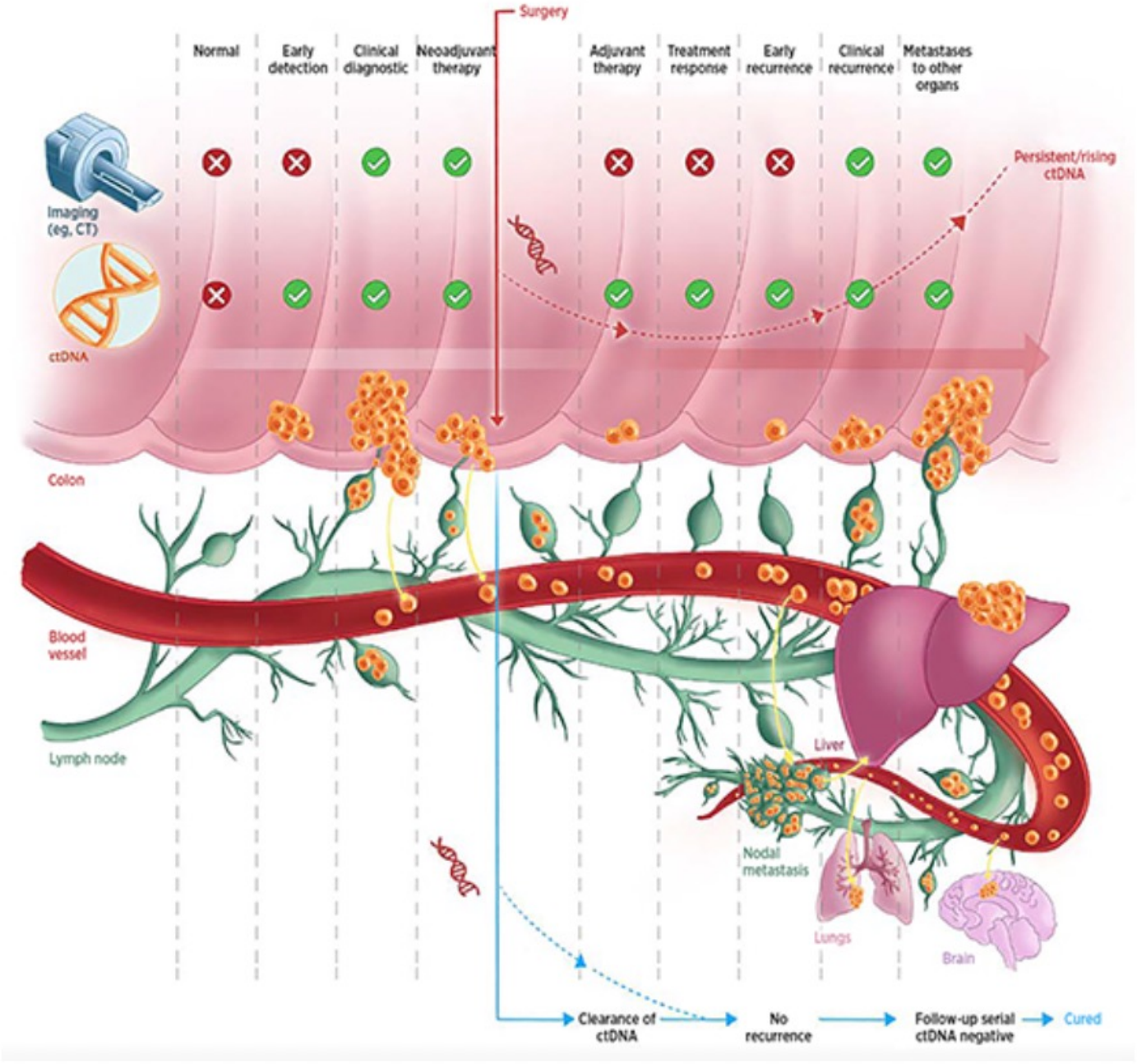


Bredno, J. et al, 2021. Clinical correlates of circulating cell-free DNA tumor fraction. PLOS ONE 16, e0256436.

Plasma MSI (microsatellite instability)

- Detected
- Not Detected (ND)

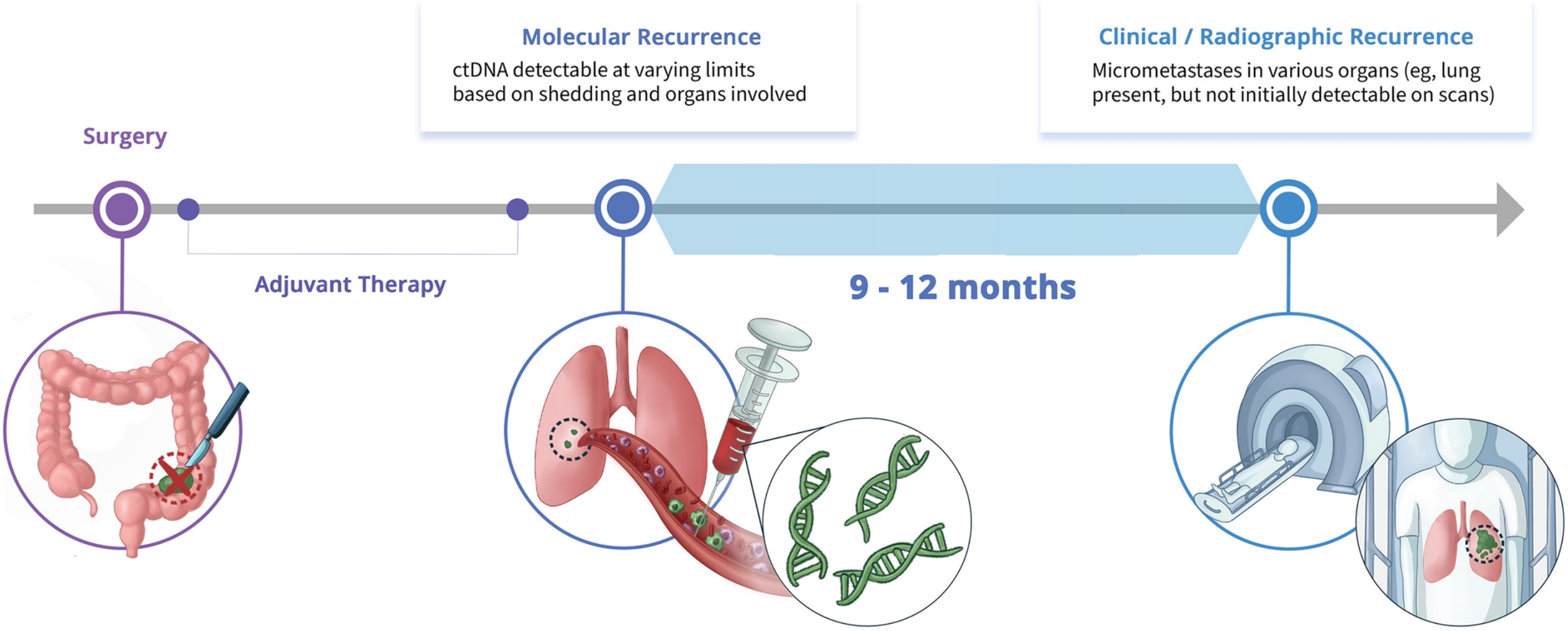




- Diagnosis
- Minimal Residual Disease
- Treatment Response
- Acquired Resistance

ASCO Daily News®

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

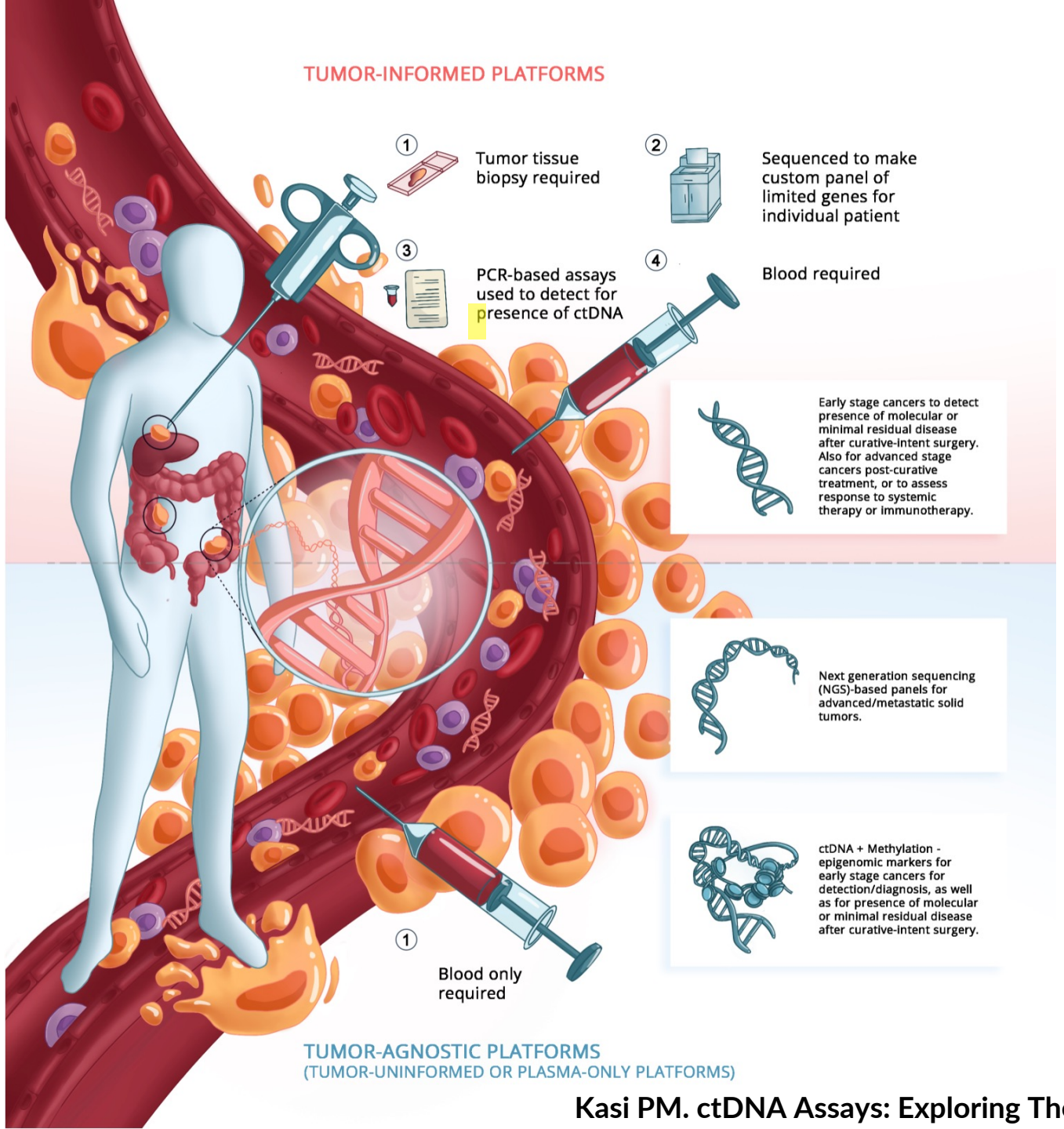


"Adjuvant-plus"

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.

NATURE REVIEWS | CLINICAL ONCOLOGY
Nat Rev Clin Oncol. 2020 Jul 6.

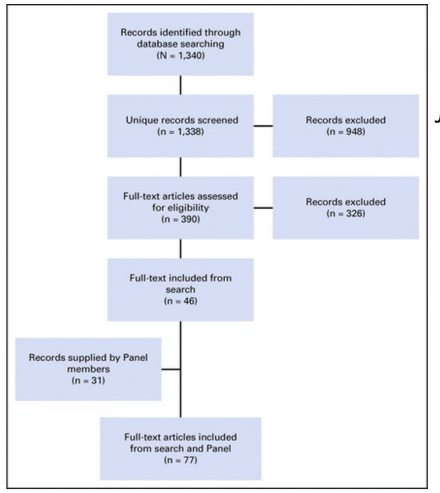
CONSENSUS STATEMENT

OPEN

Check for updates

ctDNA applications and integration in colorectal cancer: an NCI Colon and Rectal–Anal Task Forces whitepaper

Arvind Dasari[1,40]✉, Van K. Morris[1,40], Carmen J. Allegra[2], Chloe Atreya[3], Al B. Benson III[4], Patrick Boland[5], Ki Chung[6], Mehmet S. Copur[7], Ryan B. Corcoran[8], Dustin A. Deming[9], Andrea Dwyer[10], Maximilian Diehn[11], Cathy Eng[1], Thomas J. George[12], Marc J. Gollub[13], Rachel A. Goodwin[14], Stanley R. Hamilton[15], Jaclyn F. Hechtman[16], Howard Hochster[17], Theodore S. Hong[18], Federico Innocenti[19], Atif Iqbal[20], Samuel A. Jacobs[21], Hagen F. Kennecke[22], James J. Lee[23], Christopher H. Lieu[24], Heinz-Josef Lenz[25], O. Wolf Lindwasser[26], Clara Montagut[27], Bruno Odisio[28], Fang-Shu Ou[29], Laura Porter[30], Kanwal Raghav[1], Deborah Schrag[31], Aaron J. Scott[32], Qian Shi[29], John H. Strickler[33], Alan Venook[34], Rona Yaeger[35], Greg Yothers[36], Y. Nancy You[37], Jason A. Zell[38,39] and Scott Kopetz[1]



ASCO SPECIAL ARTICLE

Journal of Clinical Oncology
March 5, 2018

Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review

Merker JD. et al. *J Clin Oncol*. 2018;36:1631.

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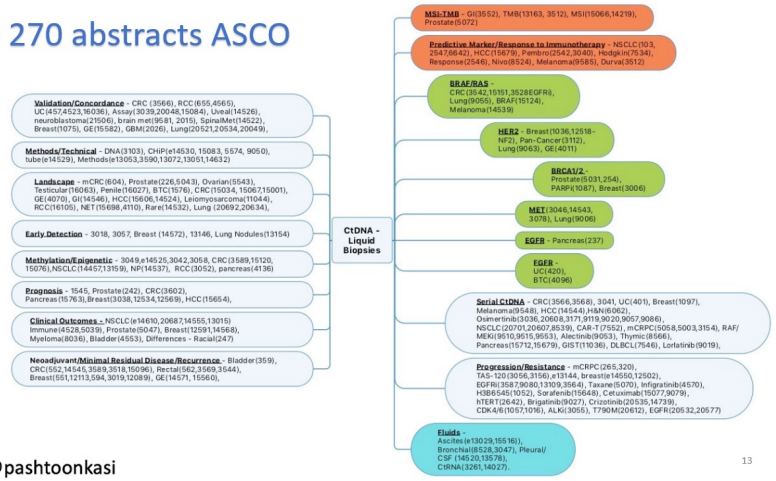
> 270 abstracts ASCO



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MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

HARVARD MEDICAL SCHOOL

cfDNA in colorectal cancer: Ready for prime time?

Ryan B. Corcoran, MD PhD
Director, Gastrointestinal Cancer Center Program
Scientific Director, Termeer Center for Targeted Therapies
Massachusetts General Hospital Cancer Center
Associate Professor of Medicine, Harvard Medical School

Applications

Identifying actionable alterations	Ready for prime time
Predicting treatment response	Soon, more trials needed
Monitoring therapeutic resistance	Ready for prime time
Detection of residual disease post-surgery	Soon, more trials needed

True Blood: Are Tumor Biopsies Obsolete?
Presented Tuesday, June 5, 2018

Is it ready for prime-time?

YES

Discussant: Heinz-Josef Lenz, MD

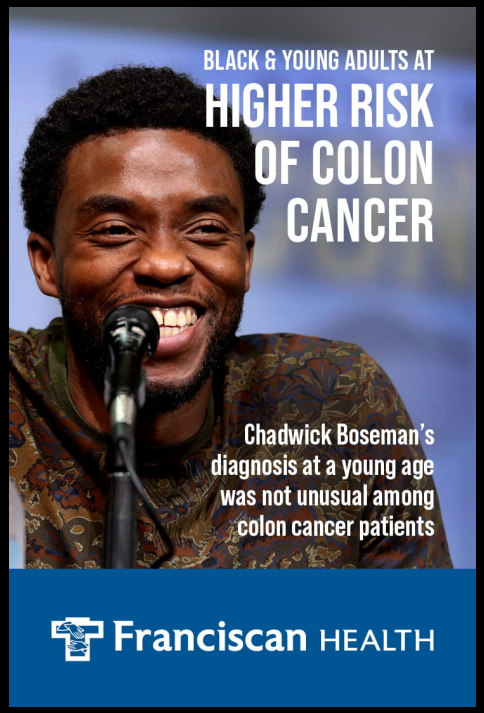
J. Terrence Lanni Chair in Gastrointestinal Cancer Research
Co-Director, USC Center for Molecular Pathway and Drug Discovery
Meeting: 2018 ASCO Annual Meeting
Session Type: Oral Abstract Session
Session Title: Gastrointestinal (Colorectal) Cancer
Track: Gastrointestinal (Colorectal) Cancer

SECTIONS HOME SEARCH

The New York Times

WELL | LIVE

More Young People Are Dying of Colon Cancer



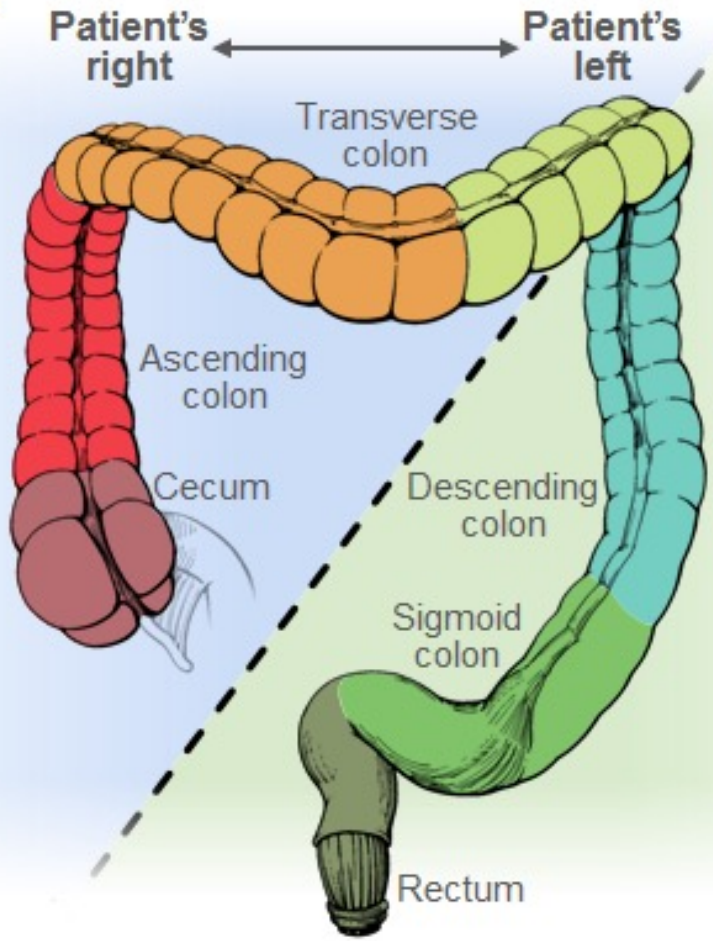
RIGHT vs. LEFT

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

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

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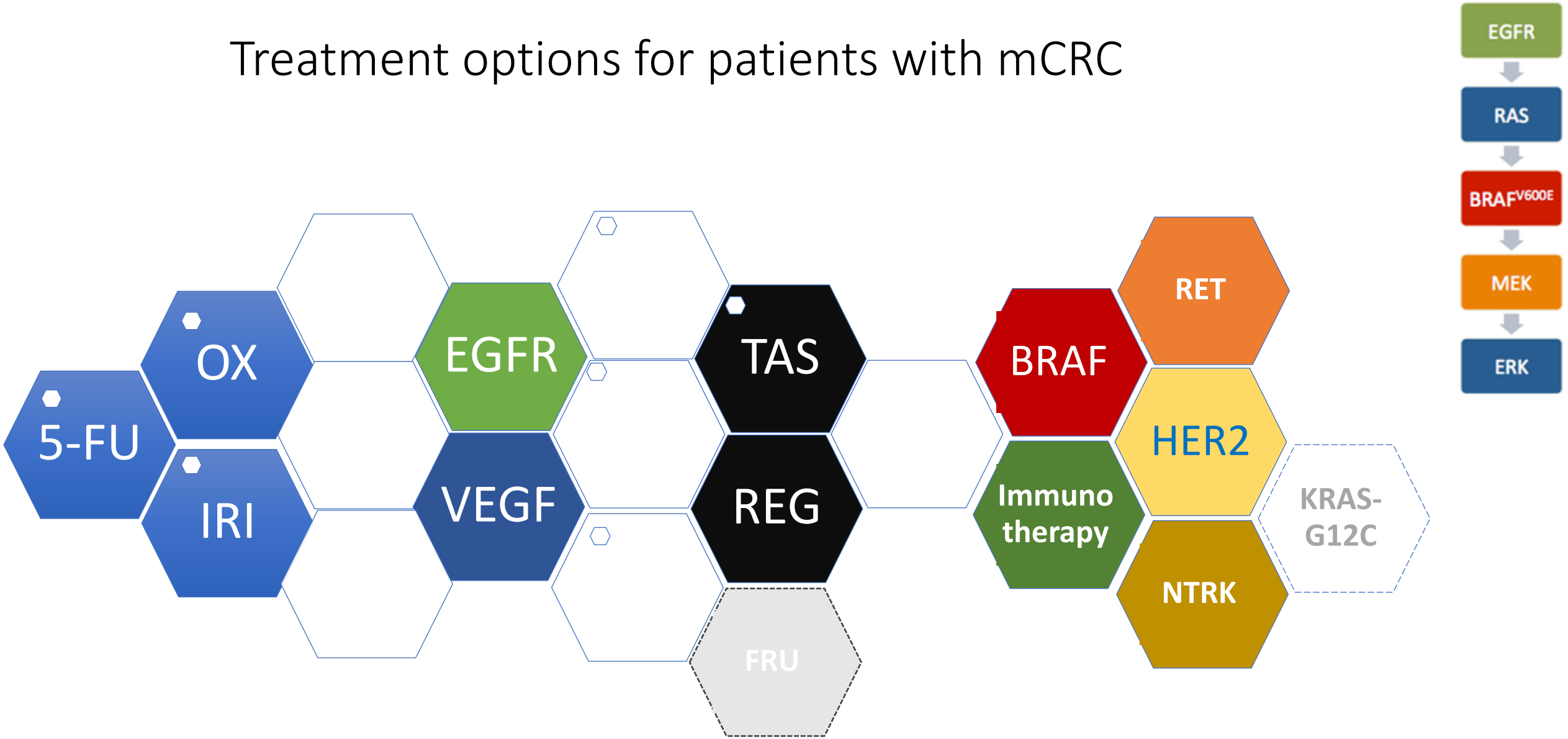
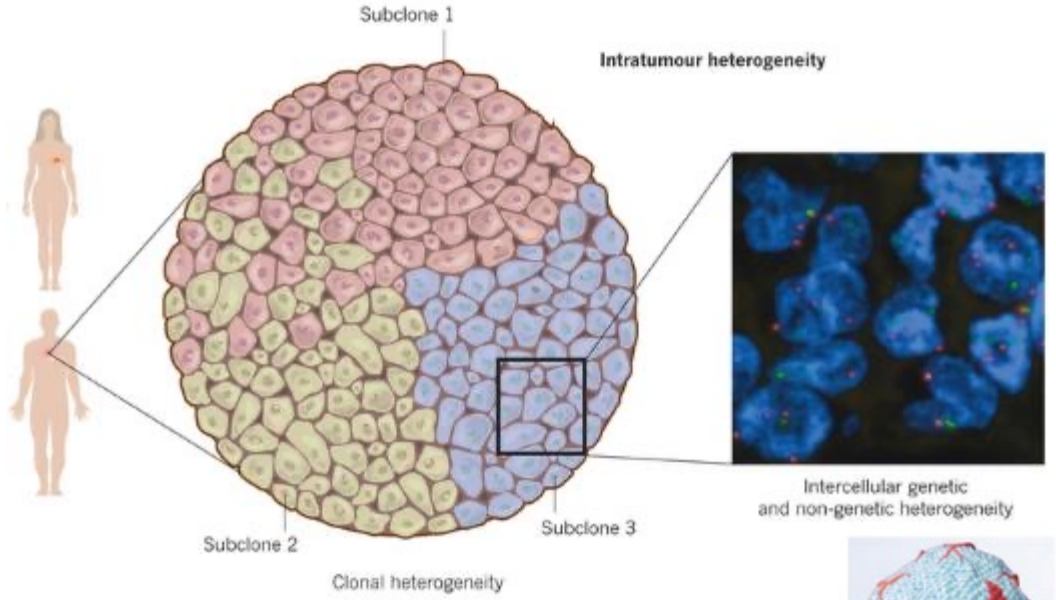
Kasi PM et al. Colorectal Cancer. Lancet Oct 2019.

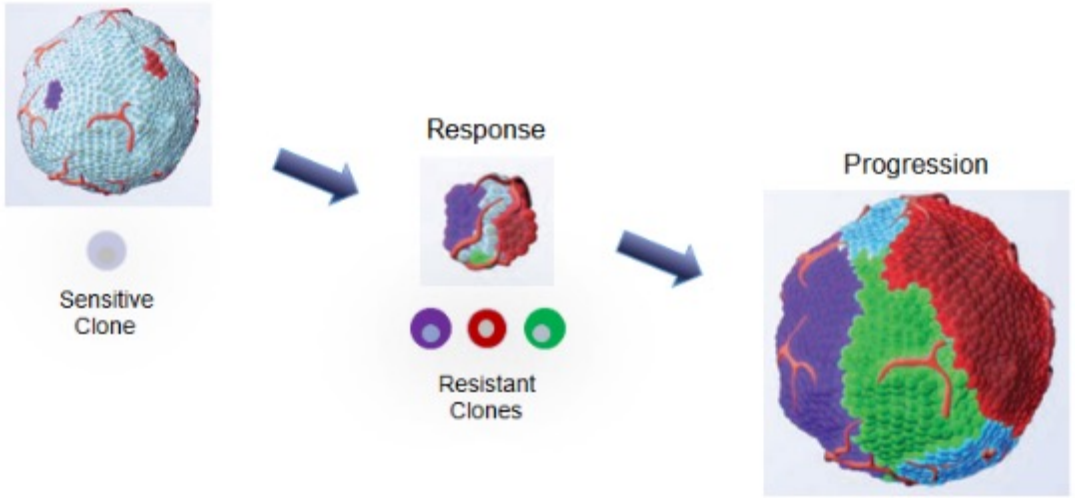
Treatment options for patients with mCRC



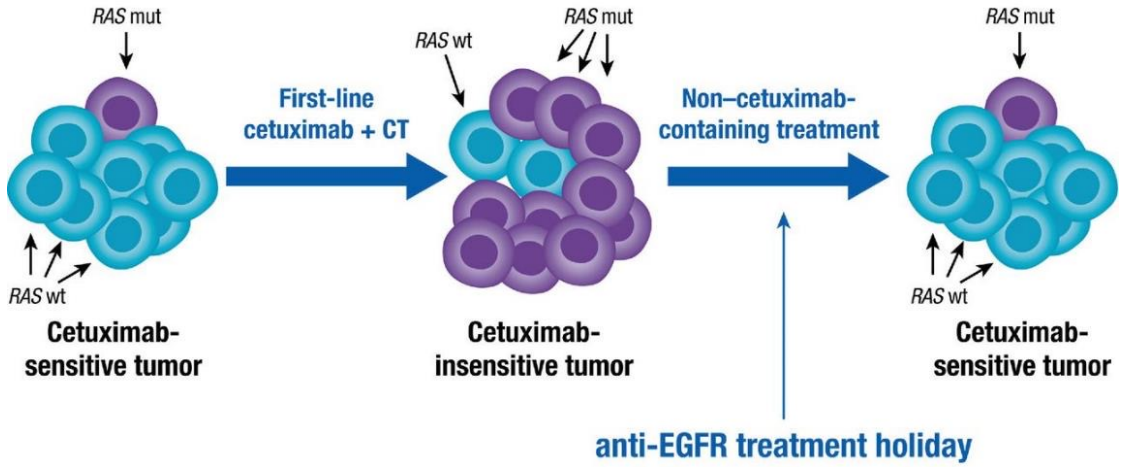
Kasi PM et al. Colorectal Cancer. Lancet Oct 2019.

Intratumoral and temporal heterogeneity



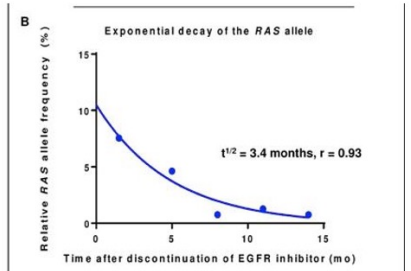


Burrell RA, et al. *Nature.* 2013;501:338.
Misale S, et al. *Cancer Discov*. 2014;4:1269.



Goldberg, et al. ESMO Open. *Cancer Horizons.* 2018 3(4).

Loss of EGFR and RAS Clones



THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

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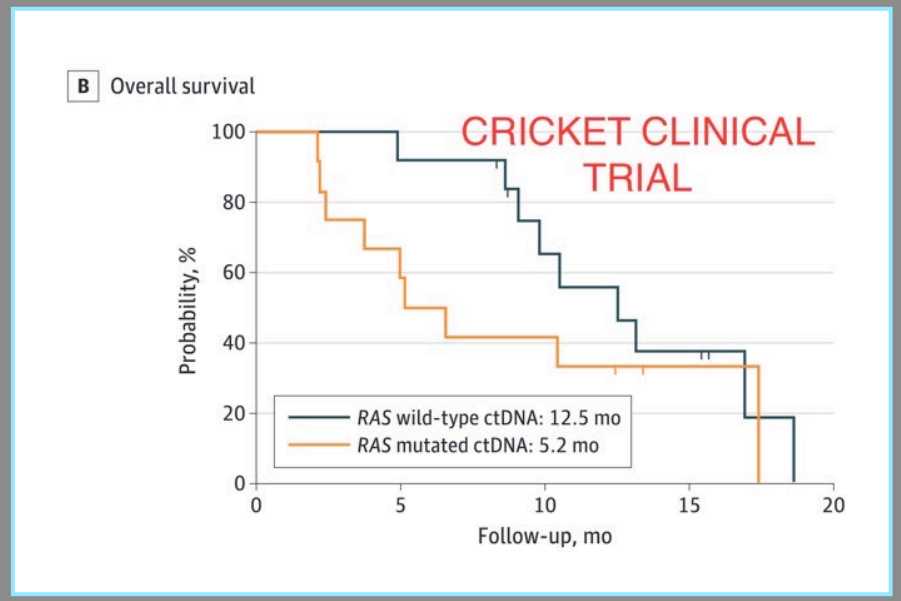
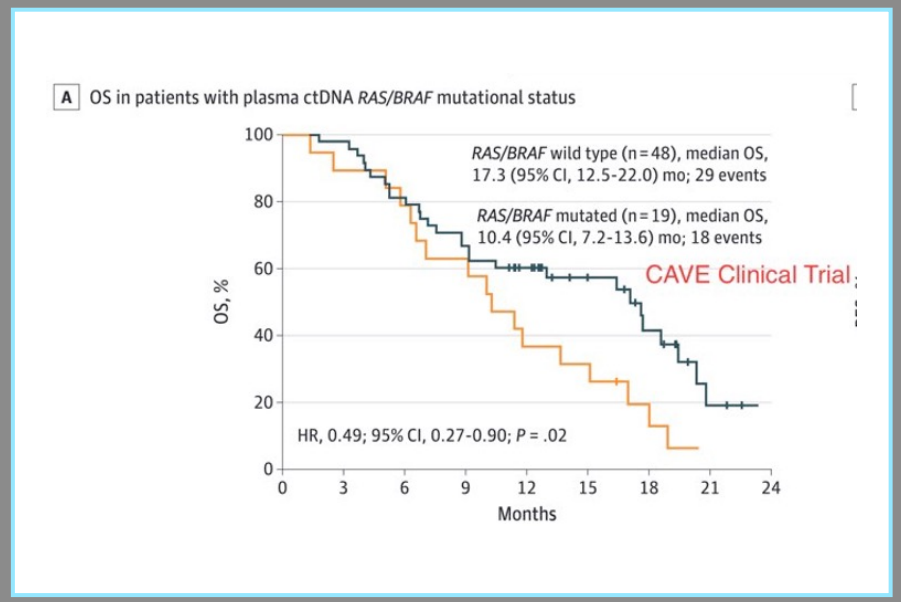
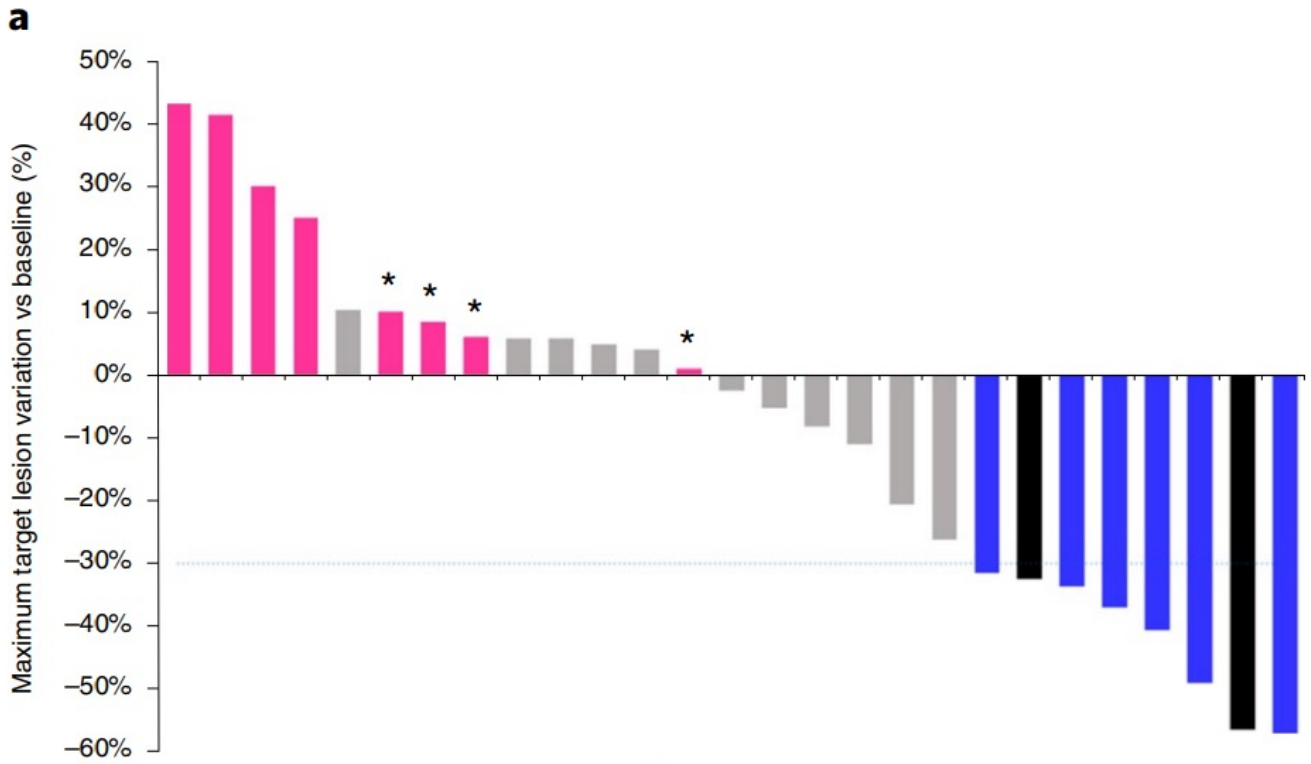
Parseghian CM, et al. *J Clin Oncol.* 36, 2018 (suppl; abstr 3511).

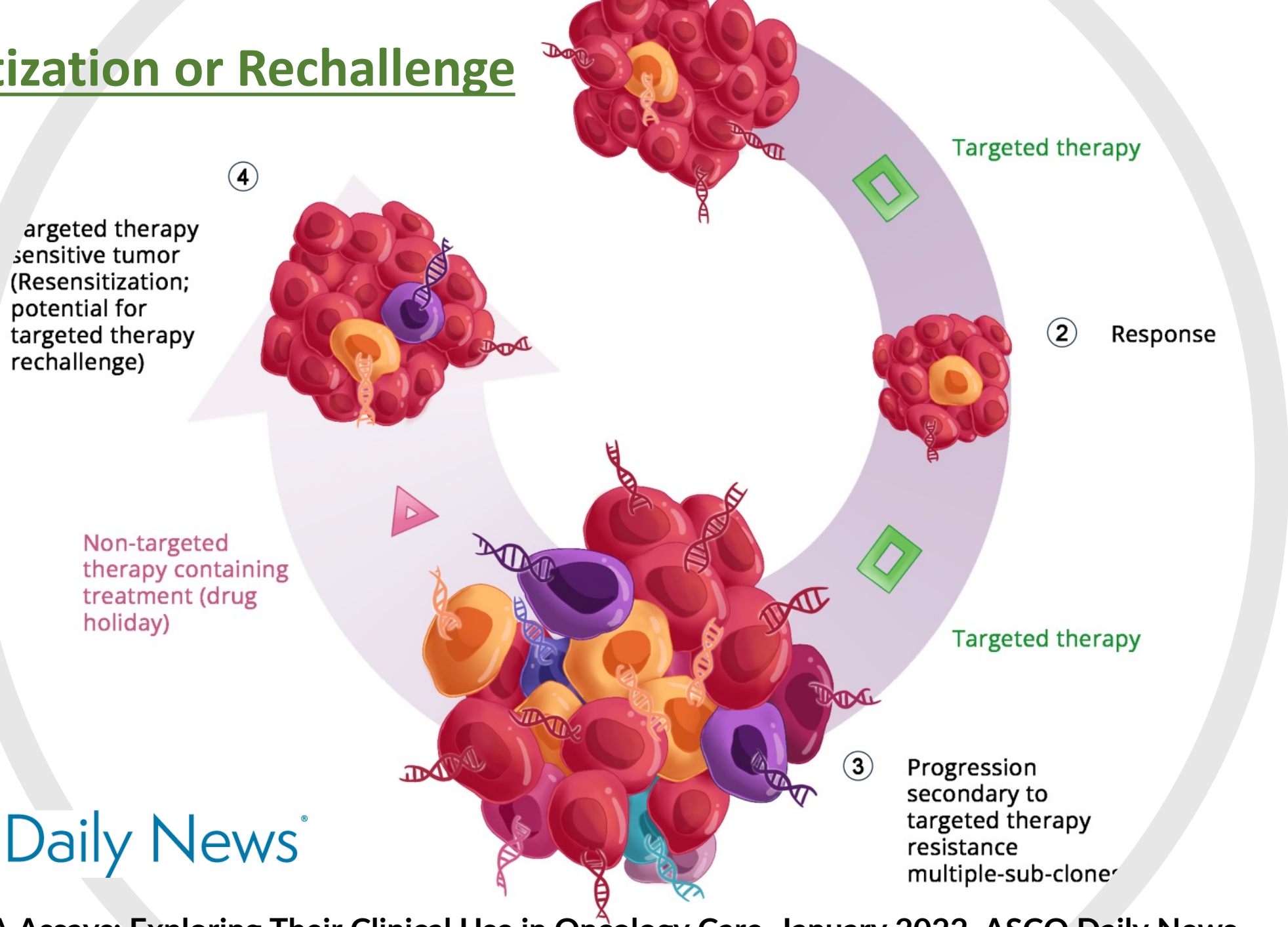




Chronos Clinical Trial



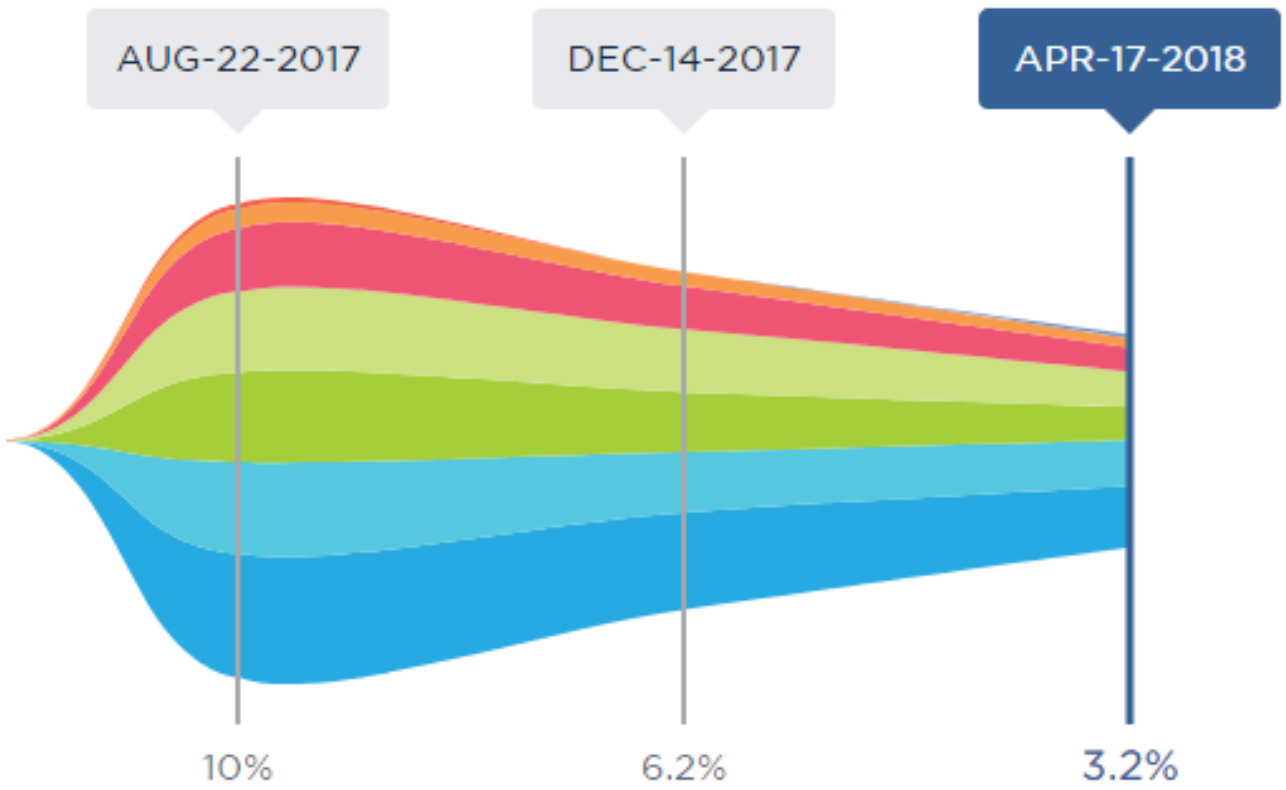
Resensitization or Rechallenge



ASCO Daily News®

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

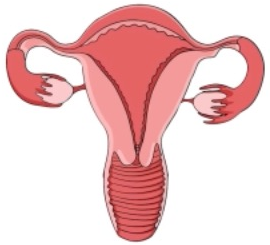
Replacement to tissue biopsy



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

Frequency of tissue insufficiency

OVARIAN CANCER [1]

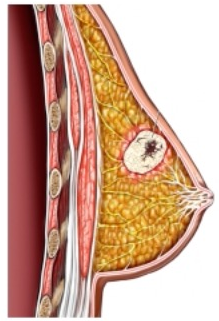


~10%

GI CANCERS [1-2]

~10%

BREAST CANCER [1-3]



~20%

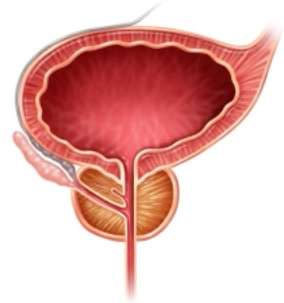
BILIARY TRACT CANCERS [4]

~25%

NSCLC [5-6]

~30%

PROSTATE CANCER [7]



~30%

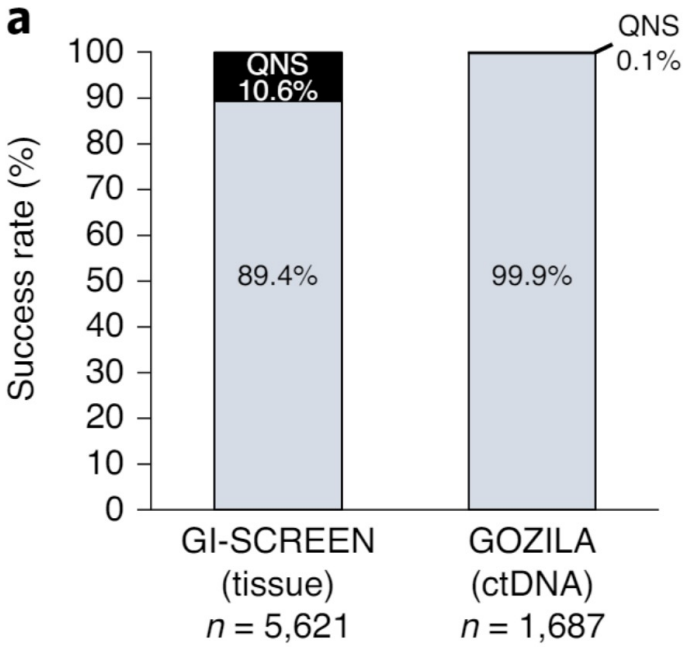
GI = gastrointestinal, NSCLC = non-small cell lung cancer

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.

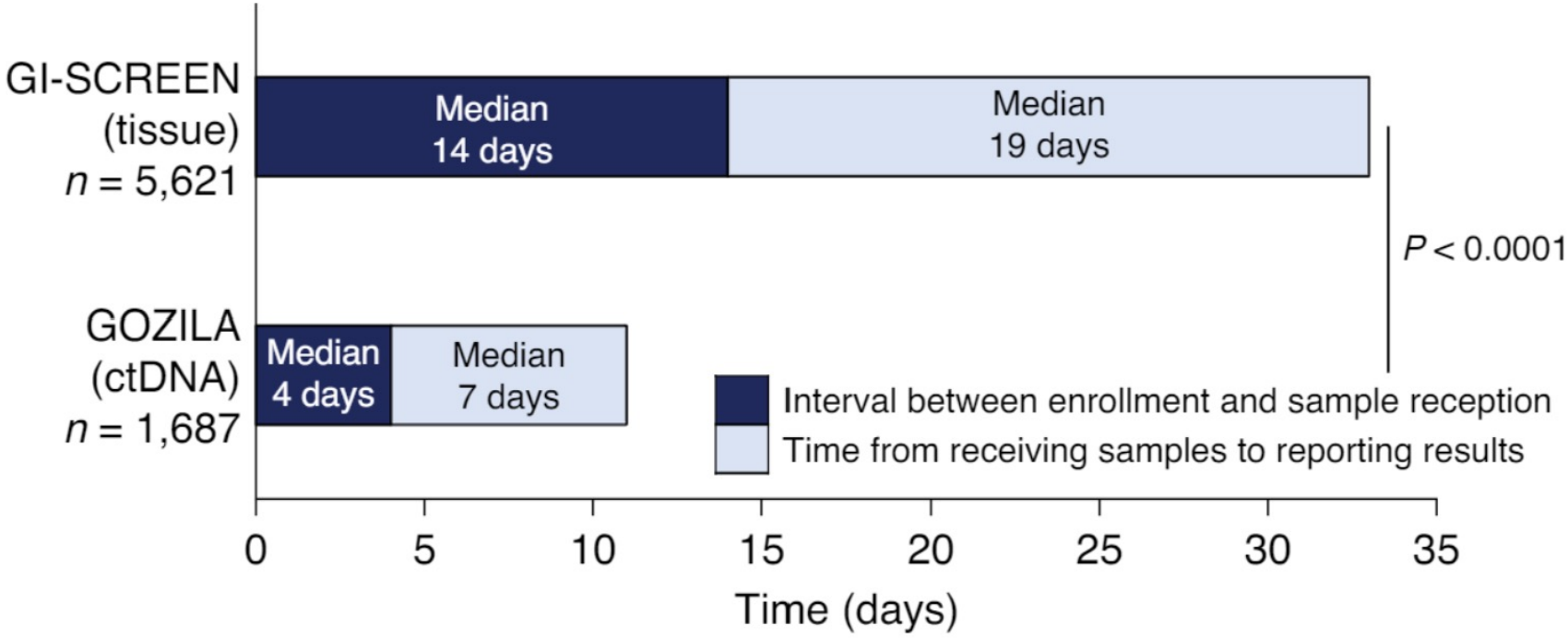
Potential Advantages of Using ctDNA Assays to Assess Actionable Mutations

- 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



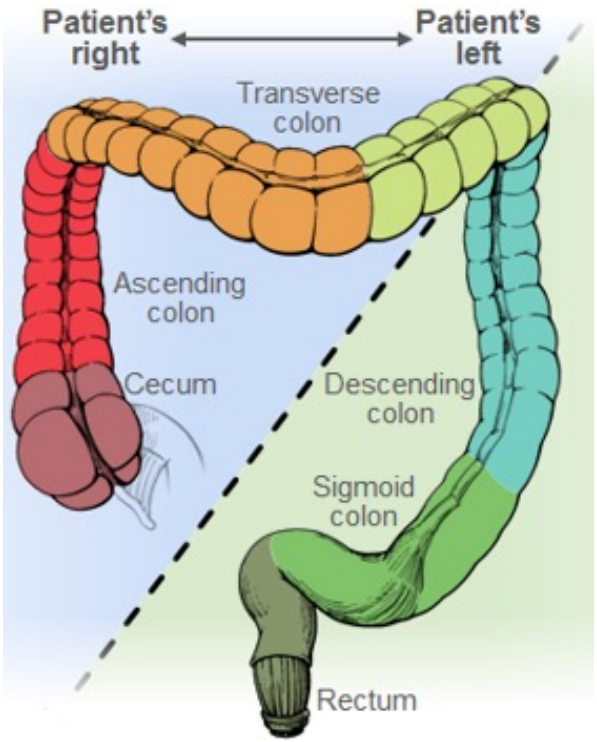
Turnround time

Nakamura. Nat Med. 2020;26:1859.

Patient Cases

Patient	41 F	VAF%
MSI	Detected	
BRAF^{V600E}	--	
RAS	KRAS^{G12D}	17.1%
HER2	--	
Other findings	BRCA2 fs MSH2 ^{LOF}	45.7% 49.8%

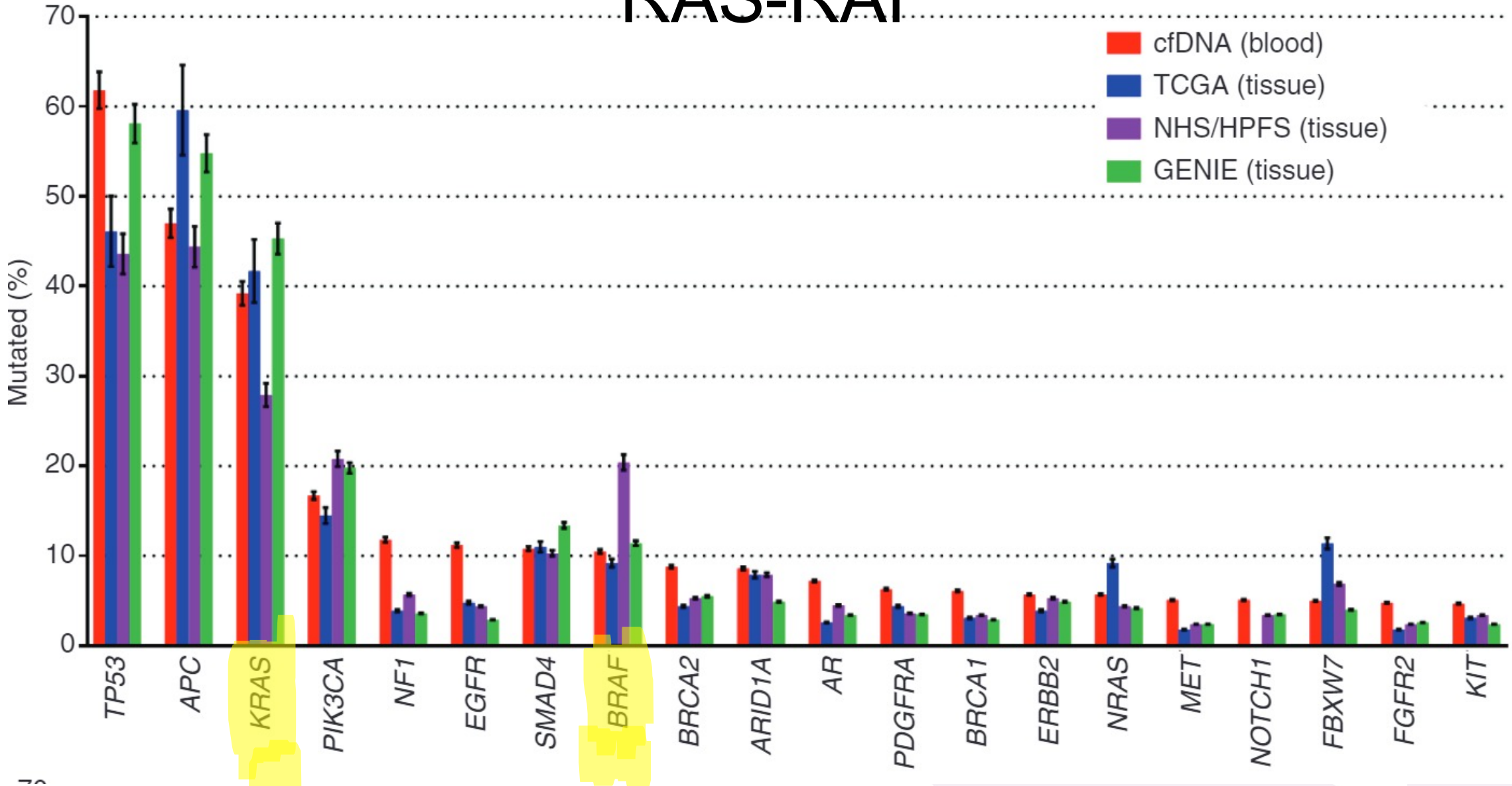
Patient	42 F	VAF%
MSI	MSS	
BRAF^{V600E}	--	
RAS	--	
HER2	--	
Other findings	APC SMAD4	30% 18%



Patient	97 F	VAF%
MSI	Detected	
BRAF^{V600E}	BRAF^{V600E}	0.8%
RAS	--	
HER2	--	
Other findings	TMB–67 MPL	 26.5%

Patient	52 F	VAF%
MSI	MSS	
BRAF^{V600E}	--	
RAS	--	
HER2	+++	CN 21
Other findings	APC TP53	26.5% 71.6%

RAS-RAF



Genomic Landscape of Cell-Free DNA in Patients with Colorectal Cancer. Cancer Discov. 2018 Feb;8(2):164-173. PMID: 29196463.

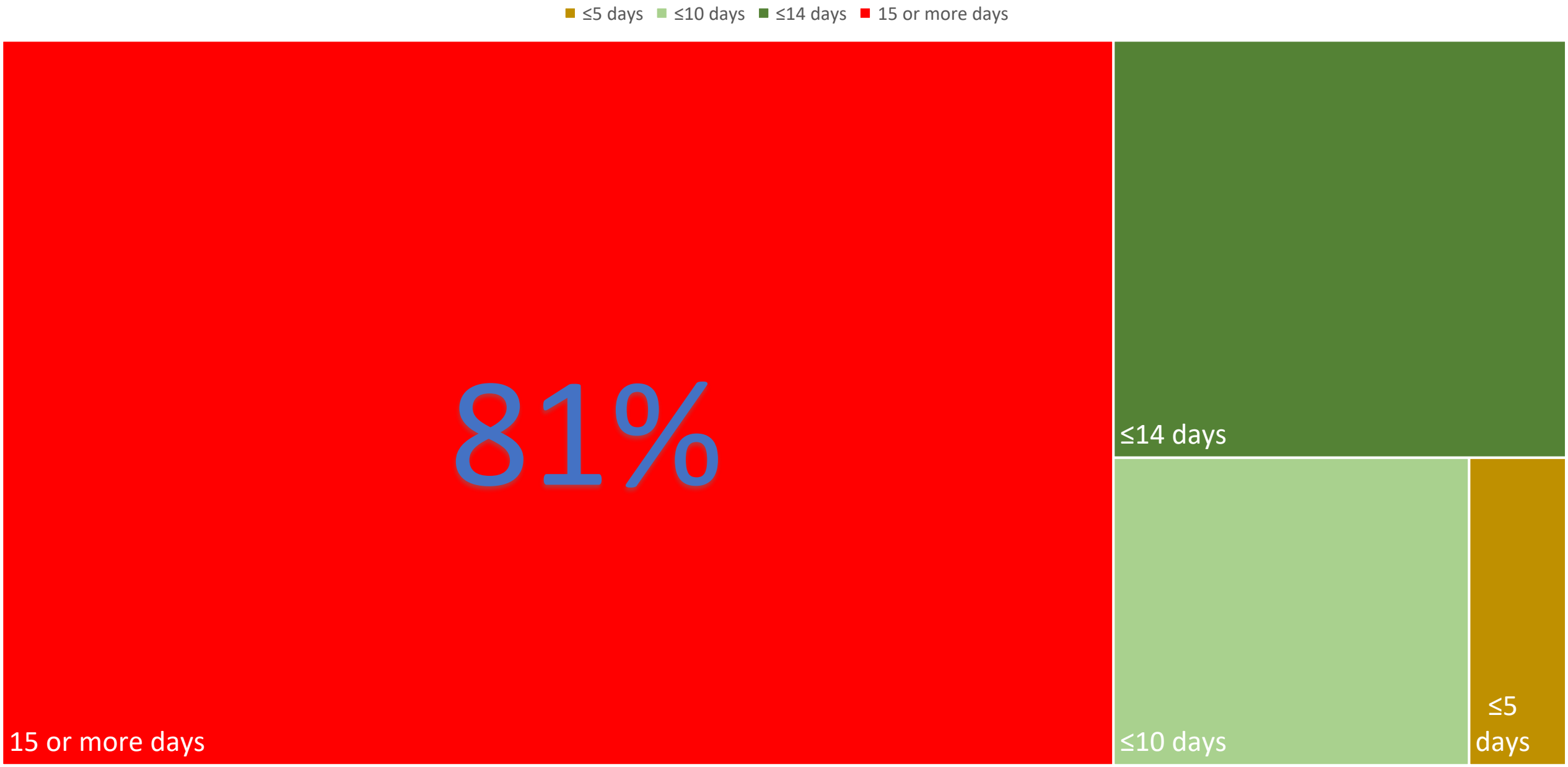
1st line Anti-EGFR therapy selection

- **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)

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.

Blood TMB or Liquid TMB (bTMB)

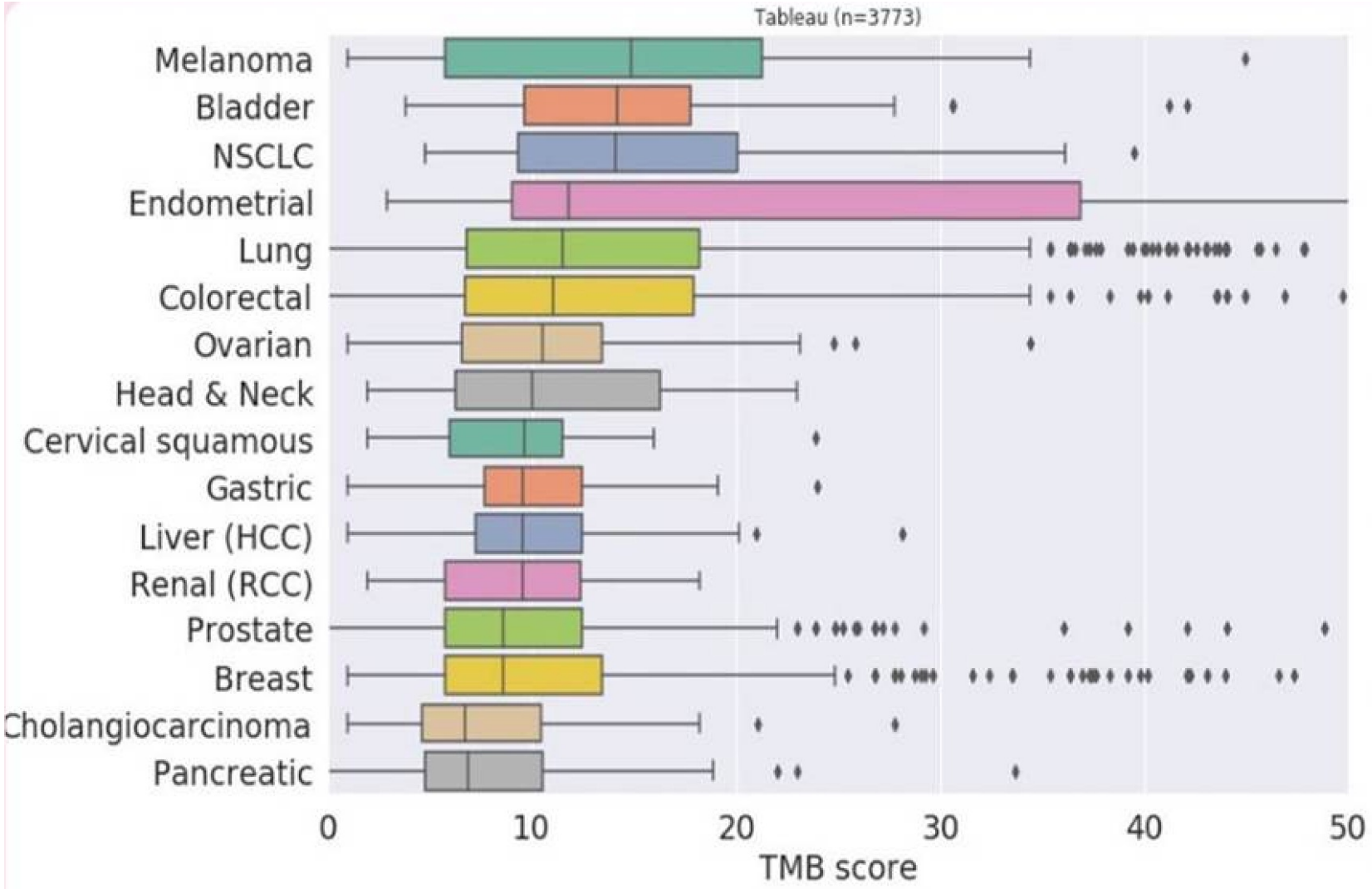
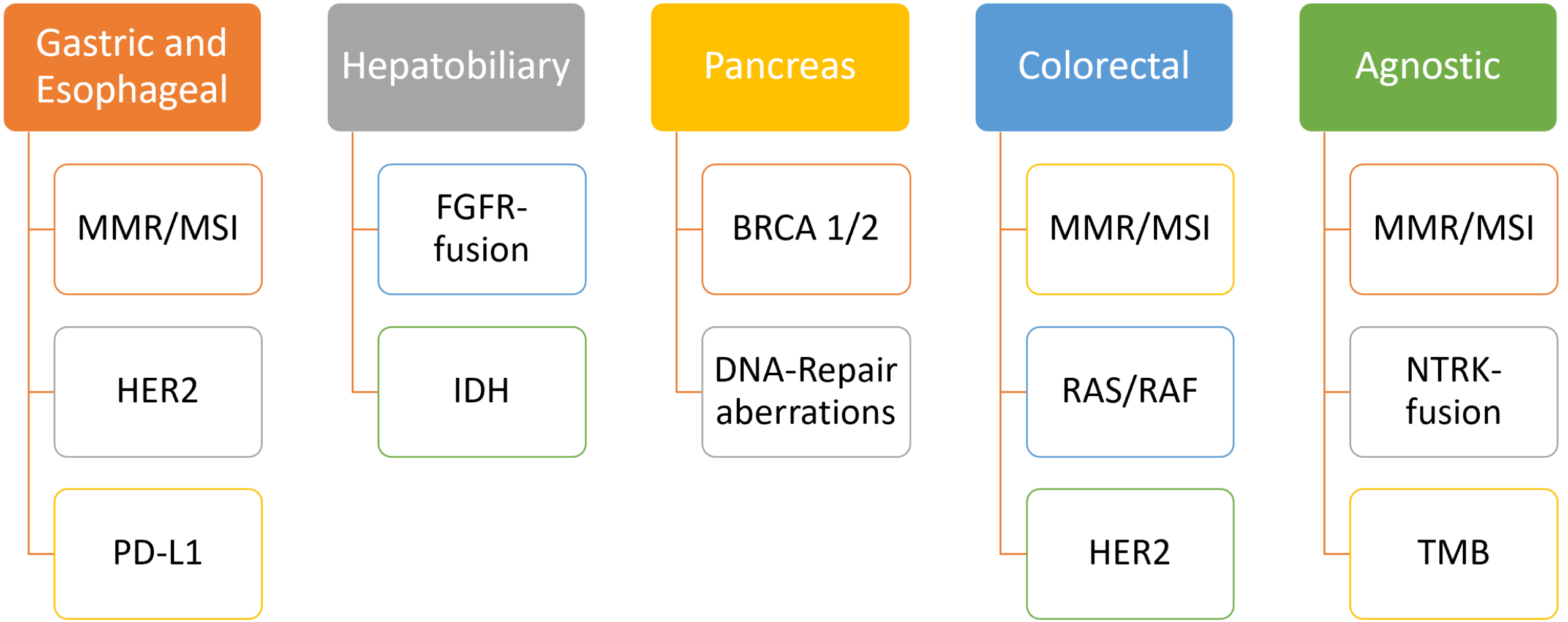


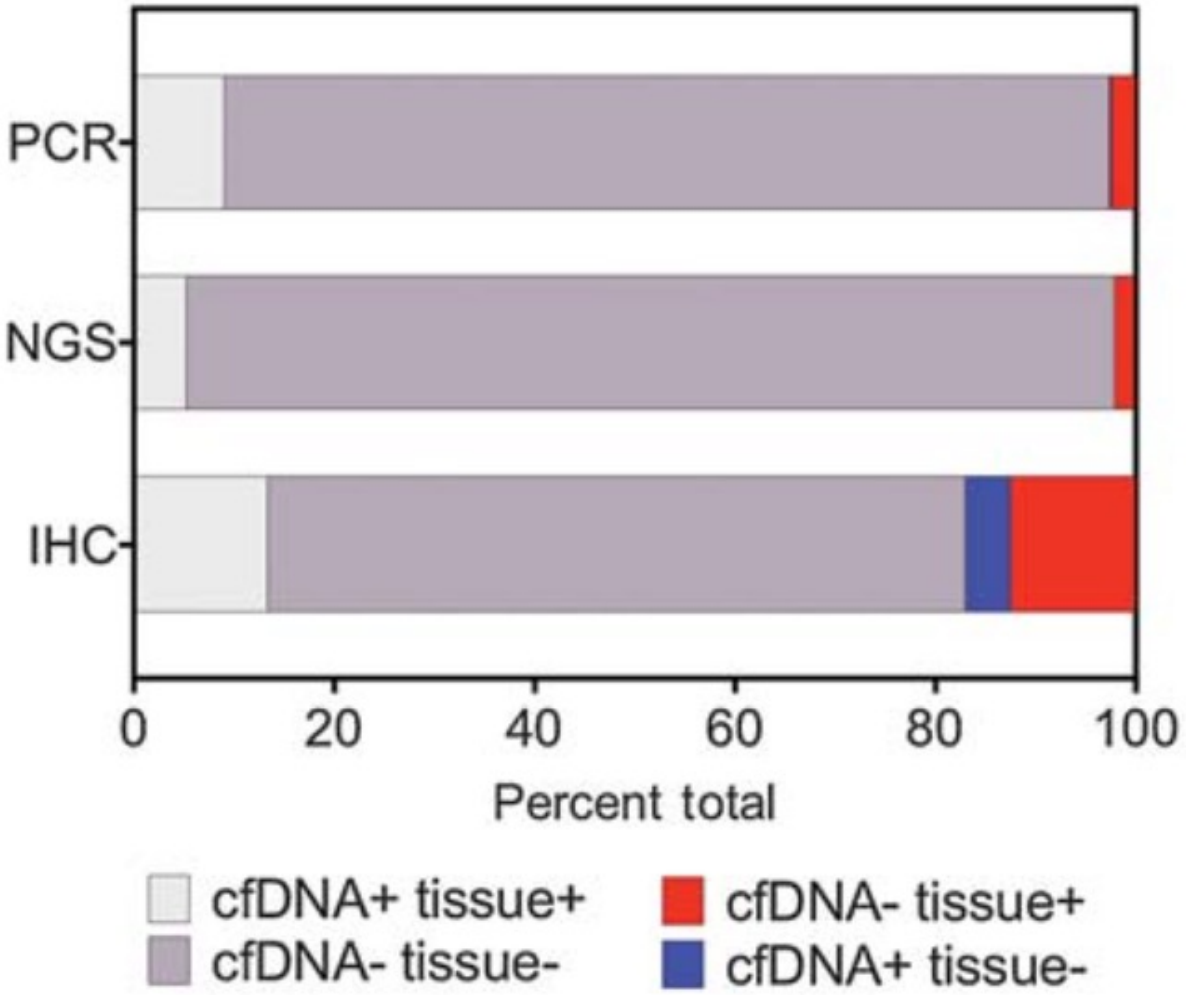
Figure 1: Distribution of blood TMB (bTMB) scores across solid tumors

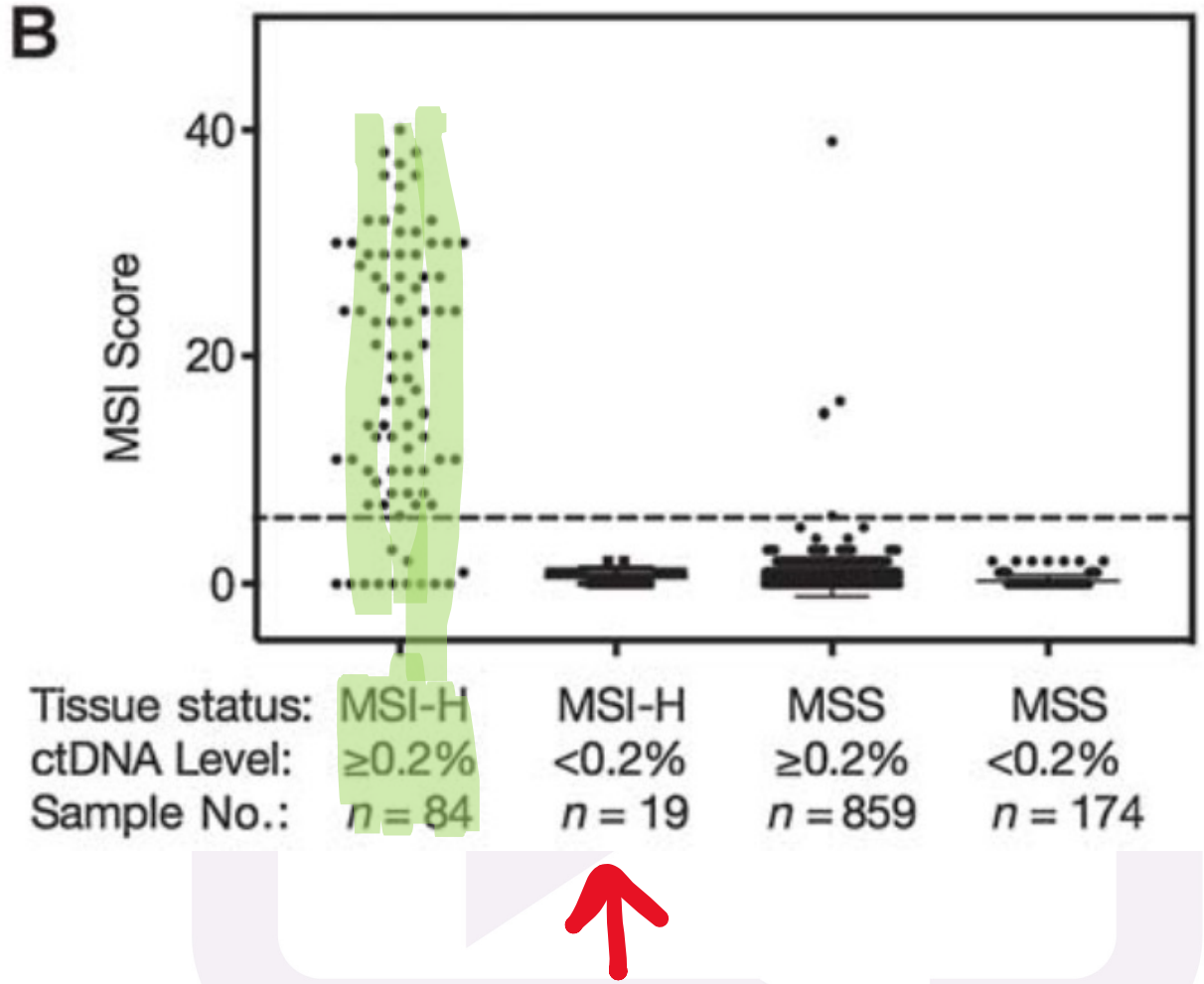
	Tumor Type	Mean TMB	Median TMB	80th percenti
	NSCLC	14.35	11.48	20.19
Gastrointestinal	Colorectal	16.49	11.03	20.1
	Liver (HCC)	10.44	9.54	13.35
	Cholangiocarcinoma	10.07	6.7	10.53
	Pancreatic	15.25	6.85	11.36
	Gastric	12.29	9.57	13.82
Genitourinary	Bladder	17.18	14.16	20.1
	Renal (RCC)	9.06	9.57	13.14
	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



Microsatellite Instability - Plasma





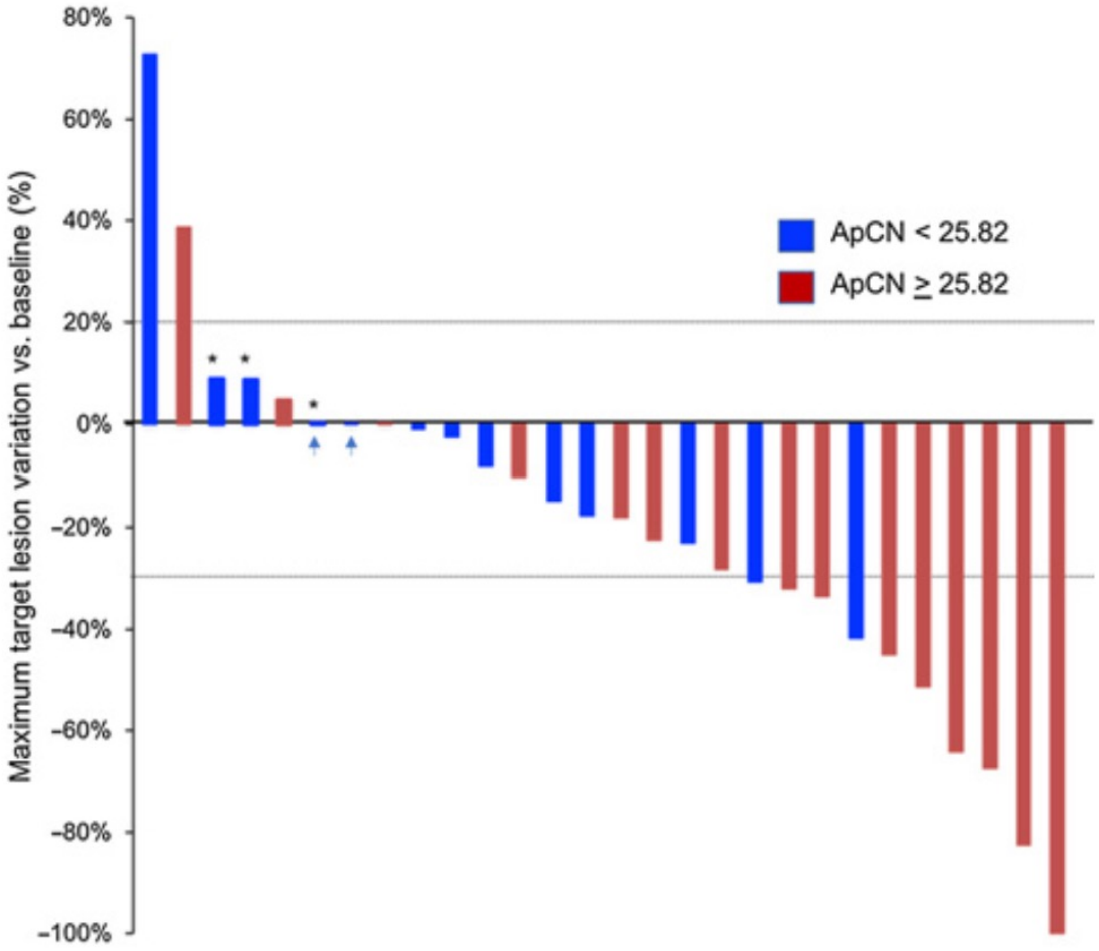
Validation of Microsatellite Instability Detection Using a Comprehensive Plasma-Based Genotyping Panel.
Clin Cancer Res. 2019 Dec 1;25(23):7035-7045. PMID: 31383735.

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



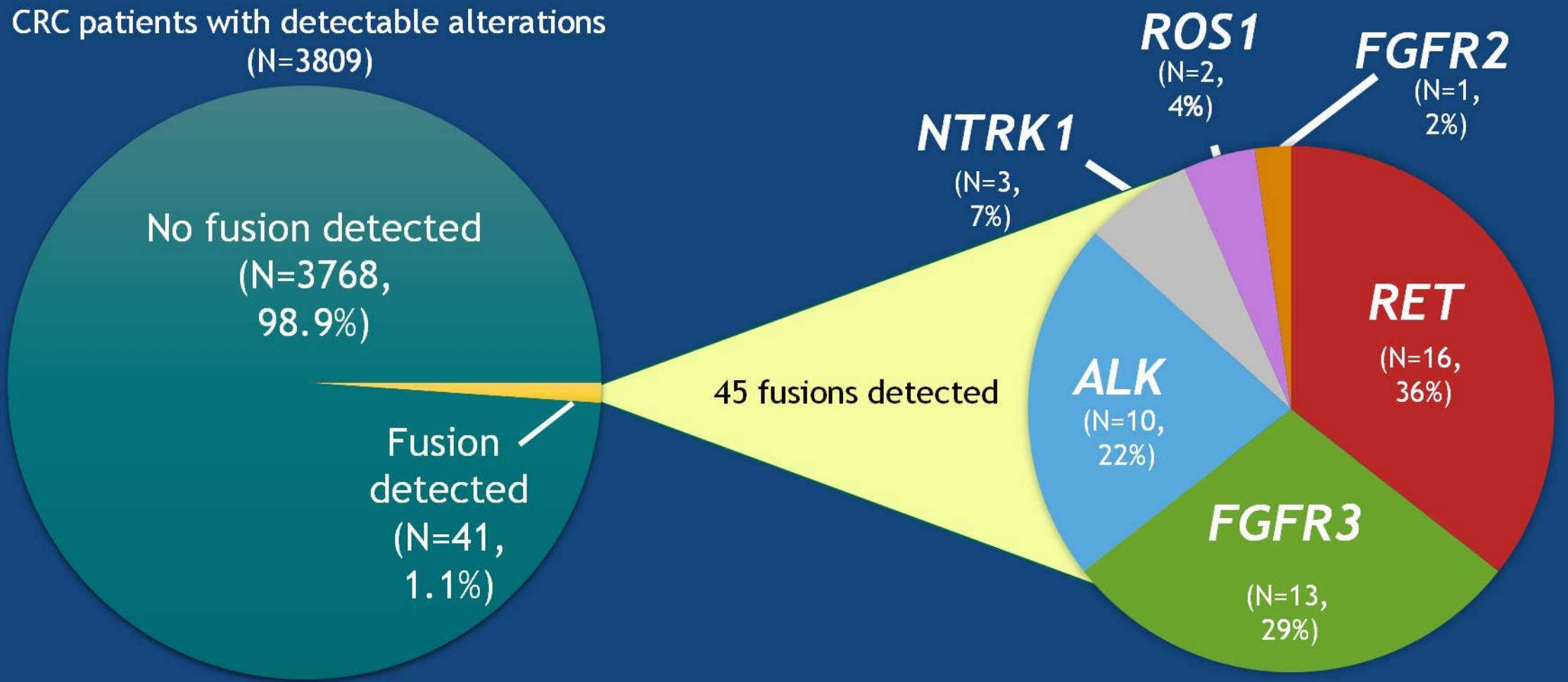
Results:

- 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.

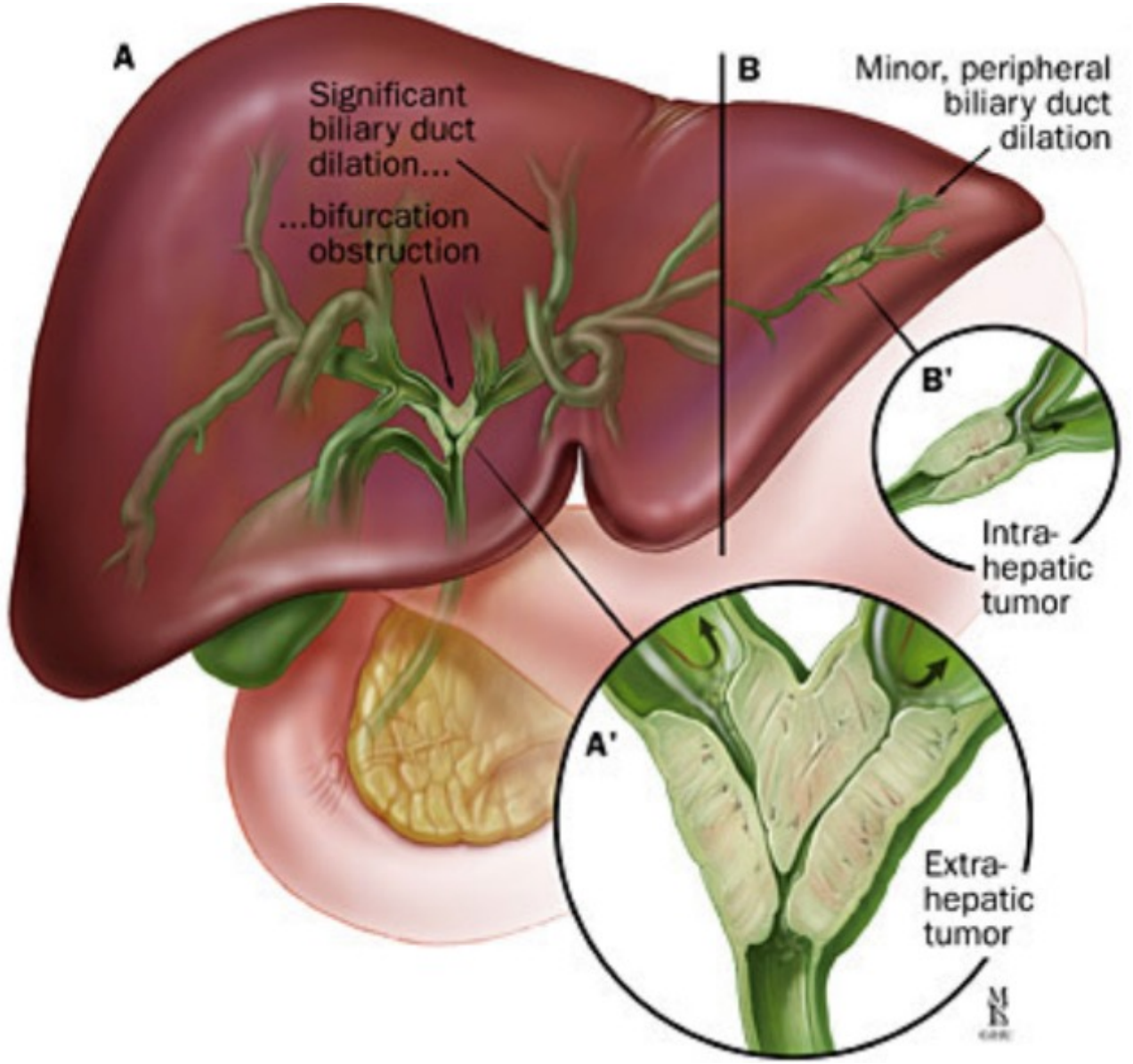
CLINICAL CANCER RESEARCH

Overall Fusion Prevalence in CRC with a ctDNA Assay

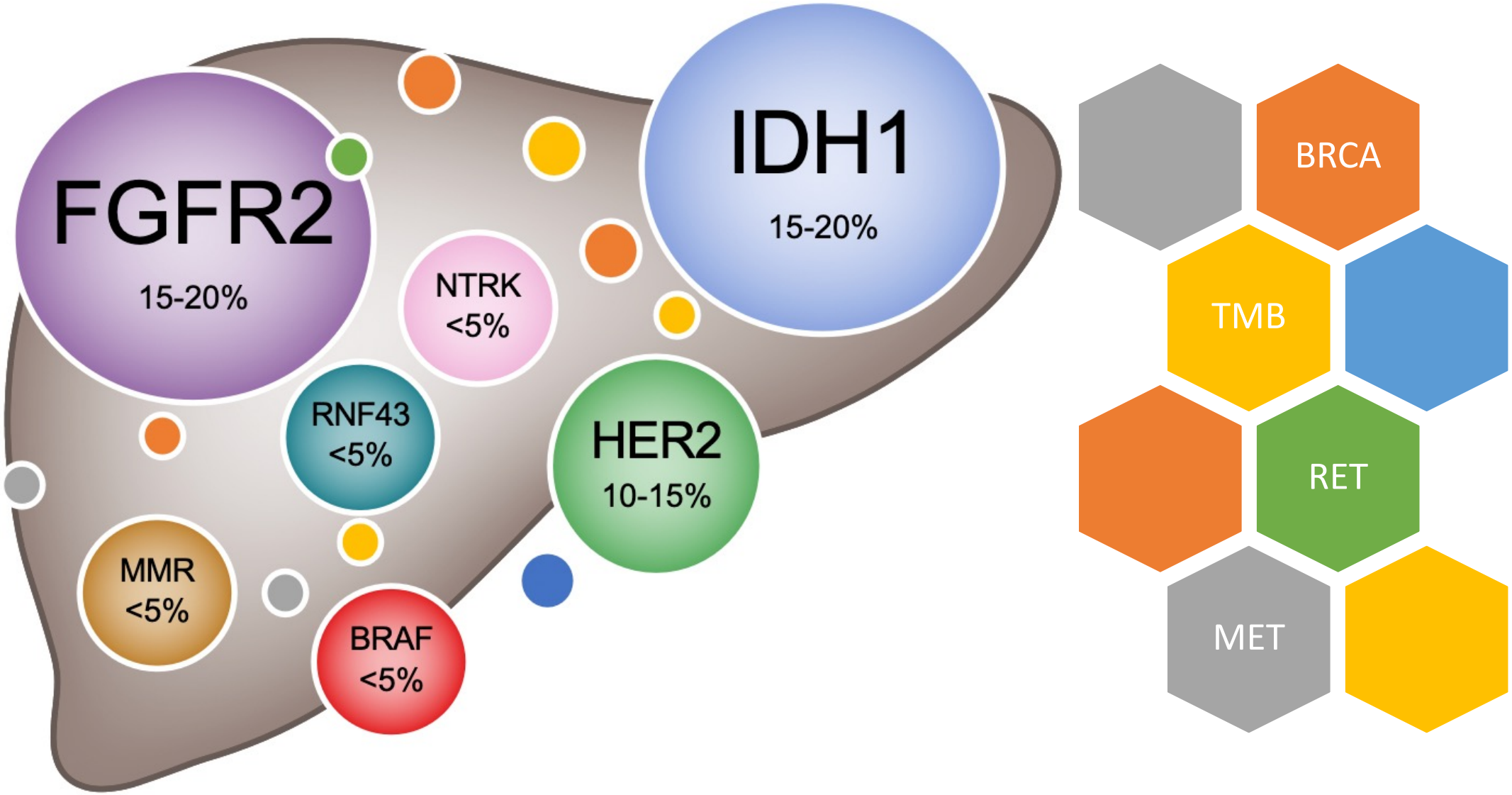


Presented By Katherine Clifton at 2018 ASCO Annual Meeting

Cholangiocarcinoma: Target-rich disease



JOHNS HOPKINS MEDICINE



Lamarca A. Molecular targeted therapies: Ready for "prime time" in biliary tract cancer. J Hepatol. 2020 Jul;73(1):170-185. PMID: 32171892.

	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.

Can we reliably use ctDNA kinetics?

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

ASCO Daily News®

Kinetics of Liquid Biopsies in Predicting Response to Immunotherapy

October 1, 2020

Pashtoon M. Kasi, MD, MS

ctDNA as a rapid surrogate of tumor response

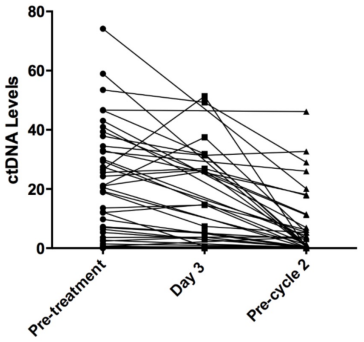
Half-life of ctDNA in circulation is measured in minutes/hours

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

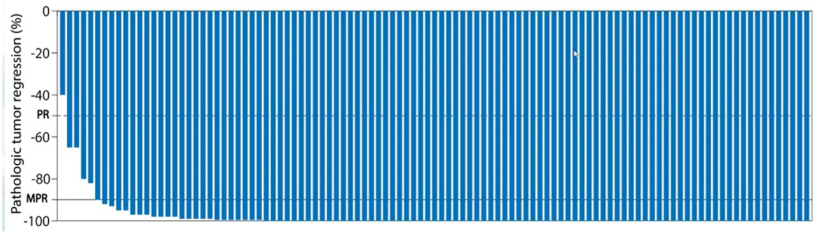
Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

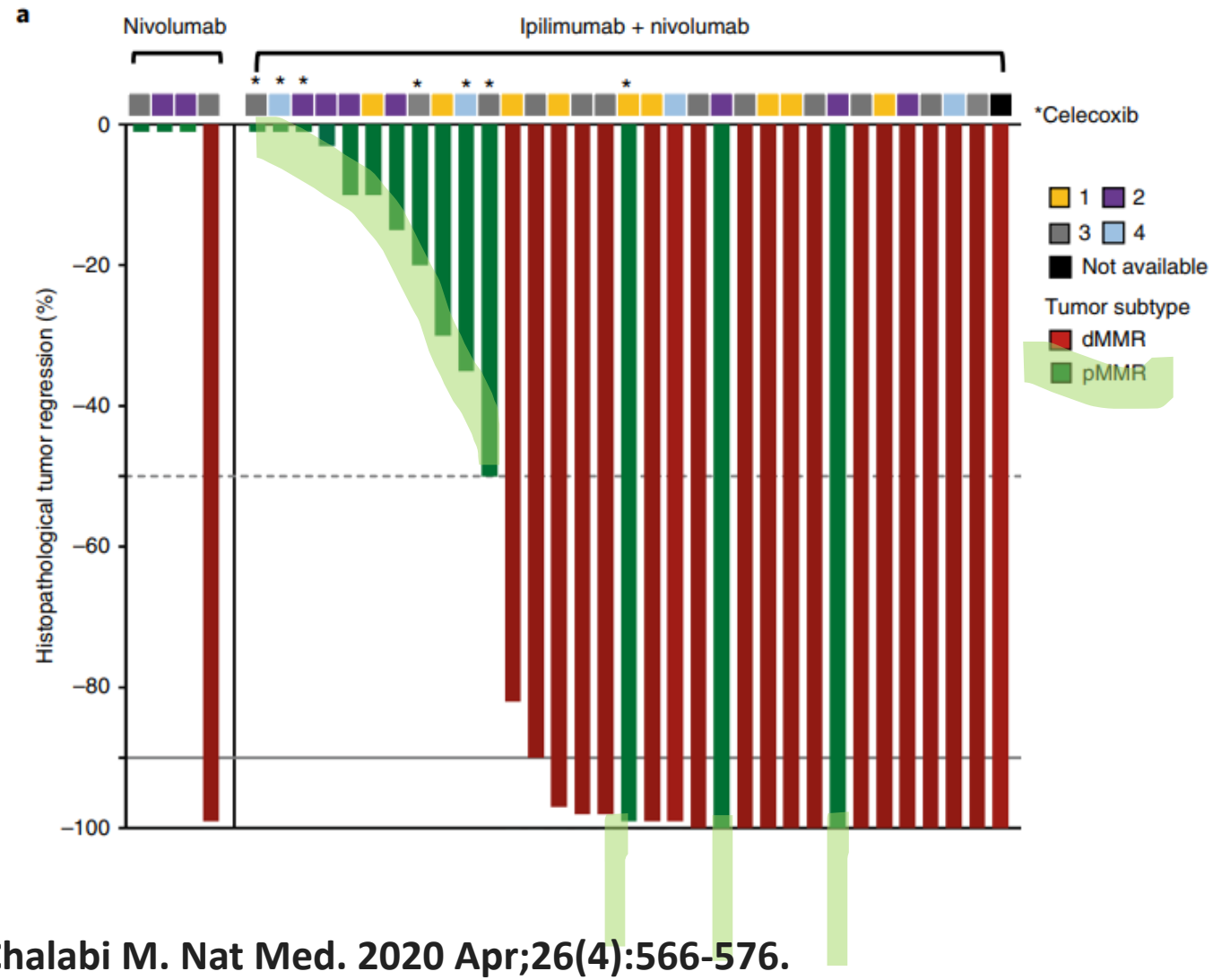
ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response
1	38	T4	N+	23.8	CR	CR	CR	cCR
2	30	T3	N+	20.5	CR	CR	CR	cCR
3	61	T1/2	N+	20.6	CR	CR	CR	cCR
4	28	T4	N+	20.5	CR	CR	CR	cCR
5	53	T1/2	N+	9.1	CR	CR	CR	cCR
6	77	T1/2	N+	11.0	CR	CR	CR	cCR
7	77	T1/2	N+	8.7	CR	CR	CR	cCR
8	55	T3	N+	5.0	CR	CR	CR	cCR
9	68	T3	N+	4.9	CR	CR	CR	cCR
10	78	T3	N-	1.7	CR	CR	CR	cCR
11	55	T3	N+	4.7	CR	CR	CR	cCR
12	27	T3	N+	4.4	CR	CR	CR	cCR
13	26	T3	N+	0.8	CR	CR	CR	cCR
14	43	T3	N+	0.7	CR	CR	CR	cCR

100%

Major pathologic response in 95% of patients; 67% pCR



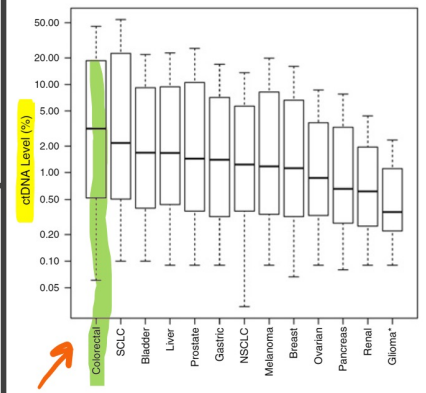
Myriam Chalabi, MD PhD, et. al, 2022 ESMO LBA7



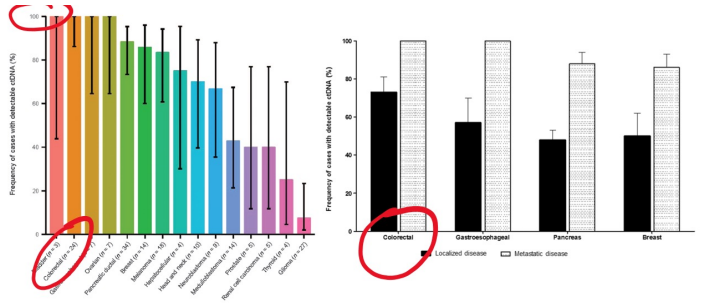
Chalabi M. Nat Med. 2020 Apr;26(4):566-576.

Does it correspond with outcomes (recurrence)?

Can we reliably detect CtDNA in patients with cancer?



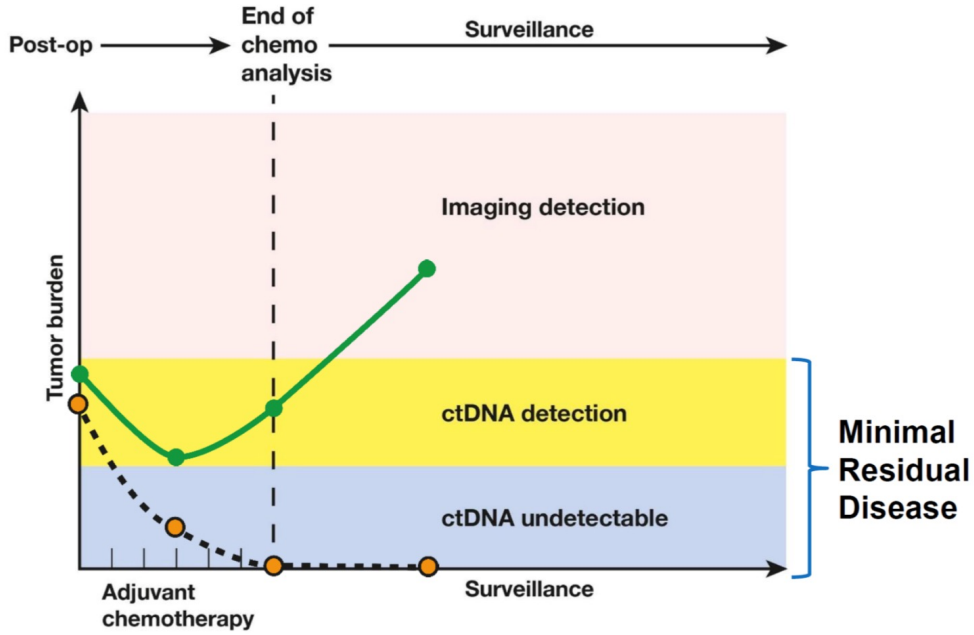
Zill OA, et al. *Clin Cancer Res*. 2018;24:3528.



- 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)

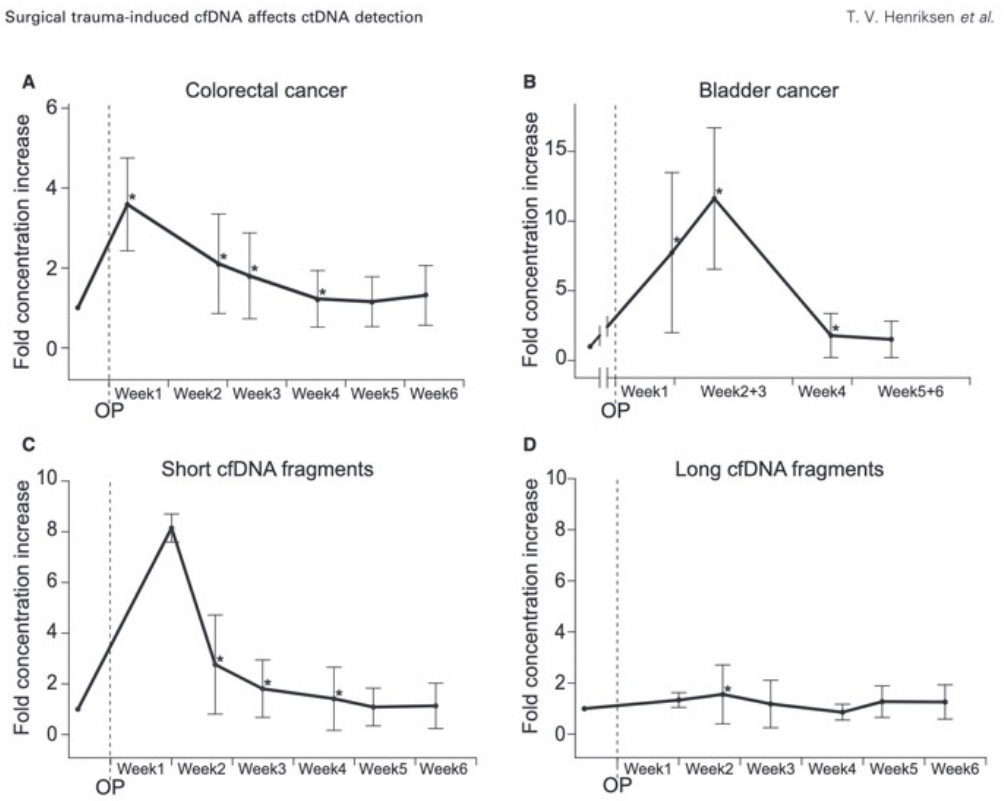
Definition of Minimal Residual Disease



Post-operative period

(background cell-free DNA cfDNA “NOISE”)

When do you need to make adjuvant therapy decisions?



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.

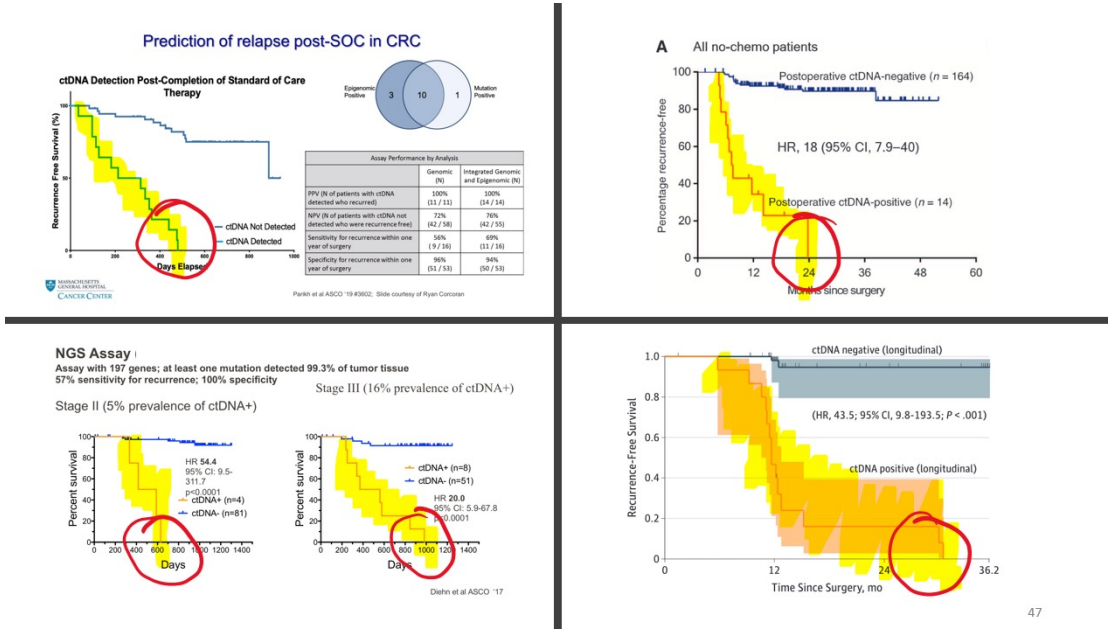
Timing is key

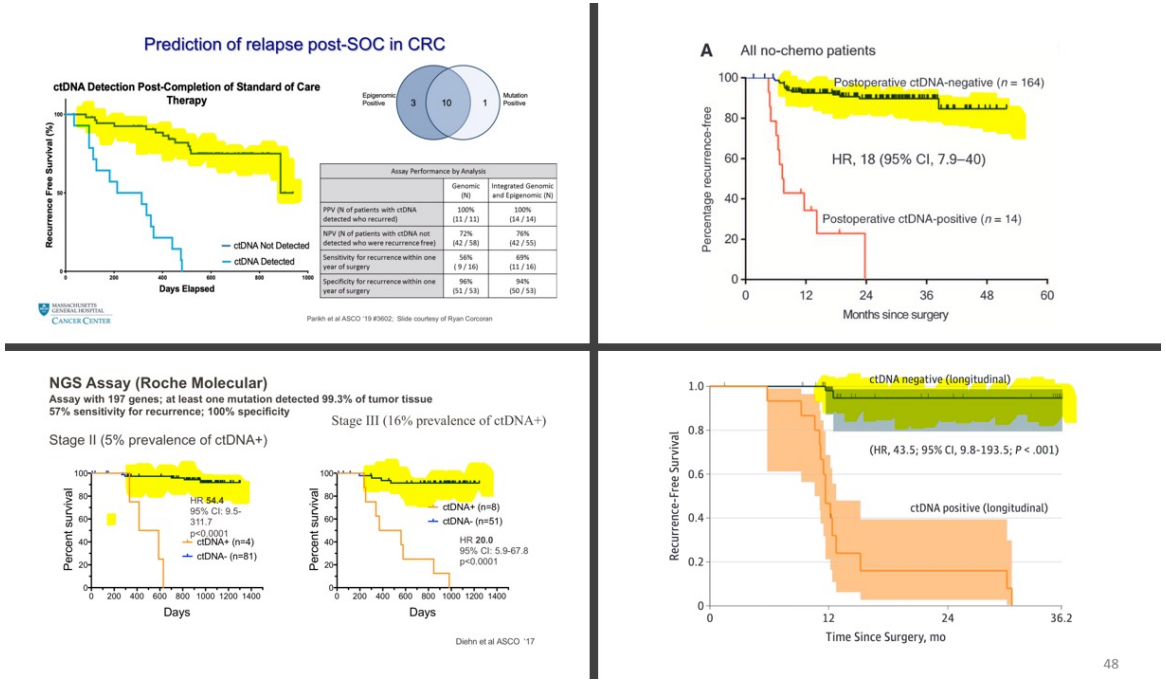
Finding the needle in the haystack

Immediate post-operative period – bigger haystack

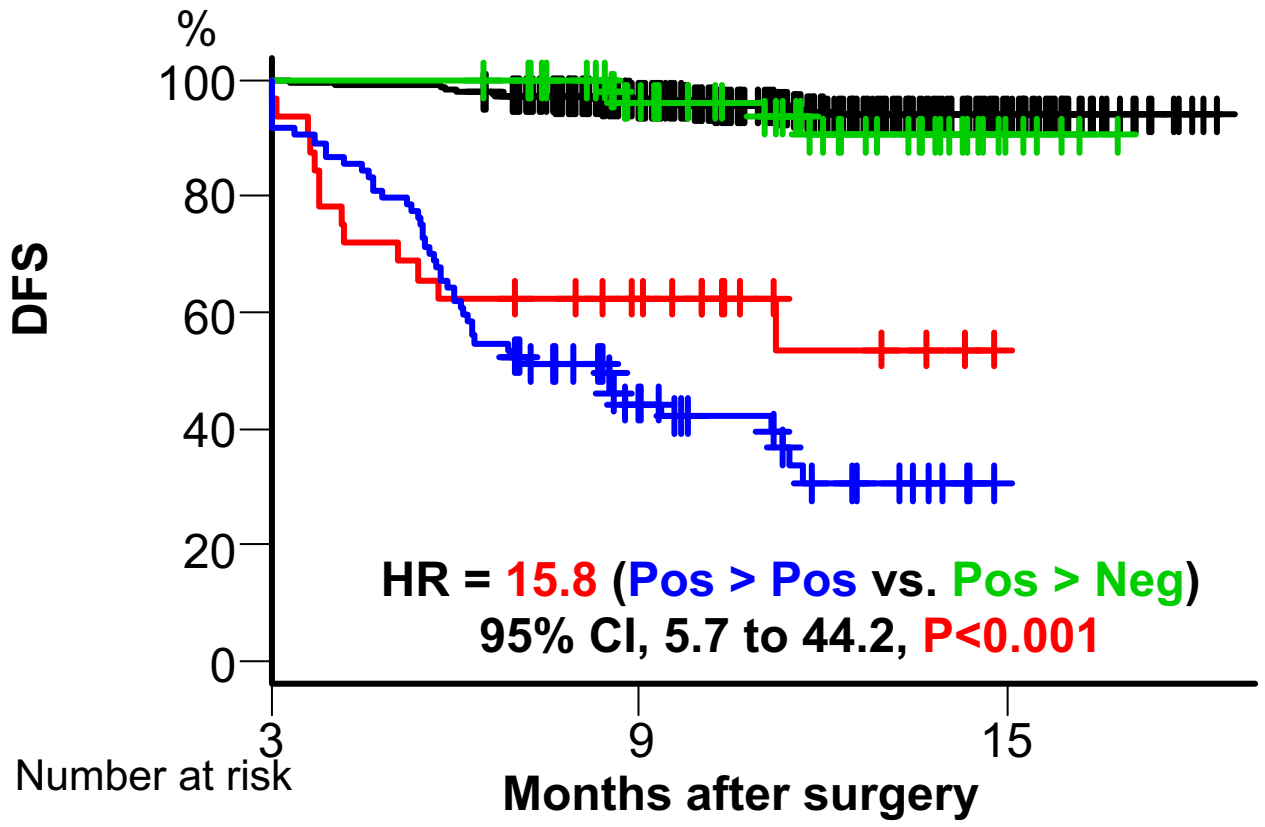
Does it correspond with outcomes (recurrence)?

What does the data look like?





DFS by ctDNA dynamics from post-op-4w to 12w



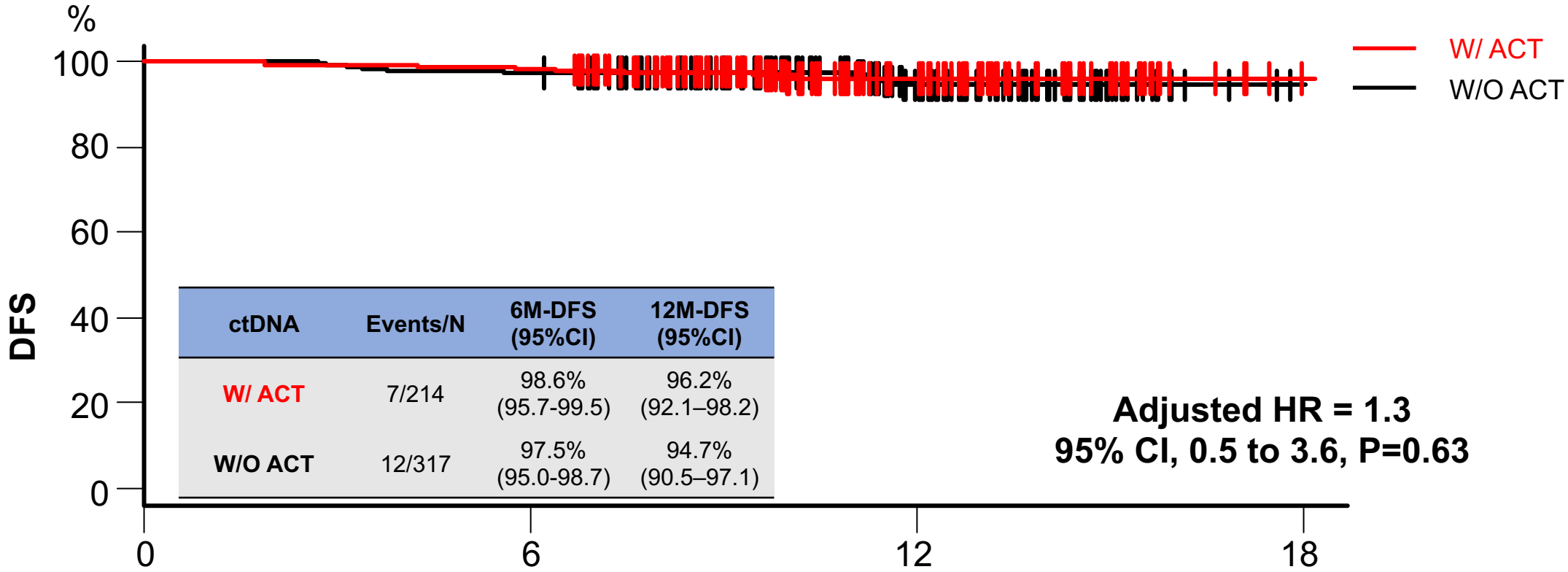
ctDNA dynamics — Neg > Neg; Neg > Pos; Pos > Neg; Pos > Pos

dynamics	Neg > Neg	Neg > Pos	Pos > Neg	Pos > Pos
Events/N	31/660	13/32	4/62	50/84
6M-DFS	98.0%	62.5%	100%	58.3%
HR	0.8	9.2	Reference	15.8
95%CI	0.27–2.15	3.0–28.4	-	5.7-44.2
P	0.60	<0.001	-	<0.001

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

Landmark analysis at the post-op-12w was performed.
DFS, disease-free survival; HR, hazard ratio; CI, confidential interval DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

DFS by ACT in post-op-4w ctDNA negative population (High-risk pStage II-III)



ctDNA	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	7/214	98.6% (95.7-99.5)	96.2% (92.1–98.2)
W/O ACT	12/317	97.5% (95.0-98.7)	94.7% (90.5–97.1)

Adjusted HR = 1.3
95% CI, 0.5 to 3.6, P=0.63

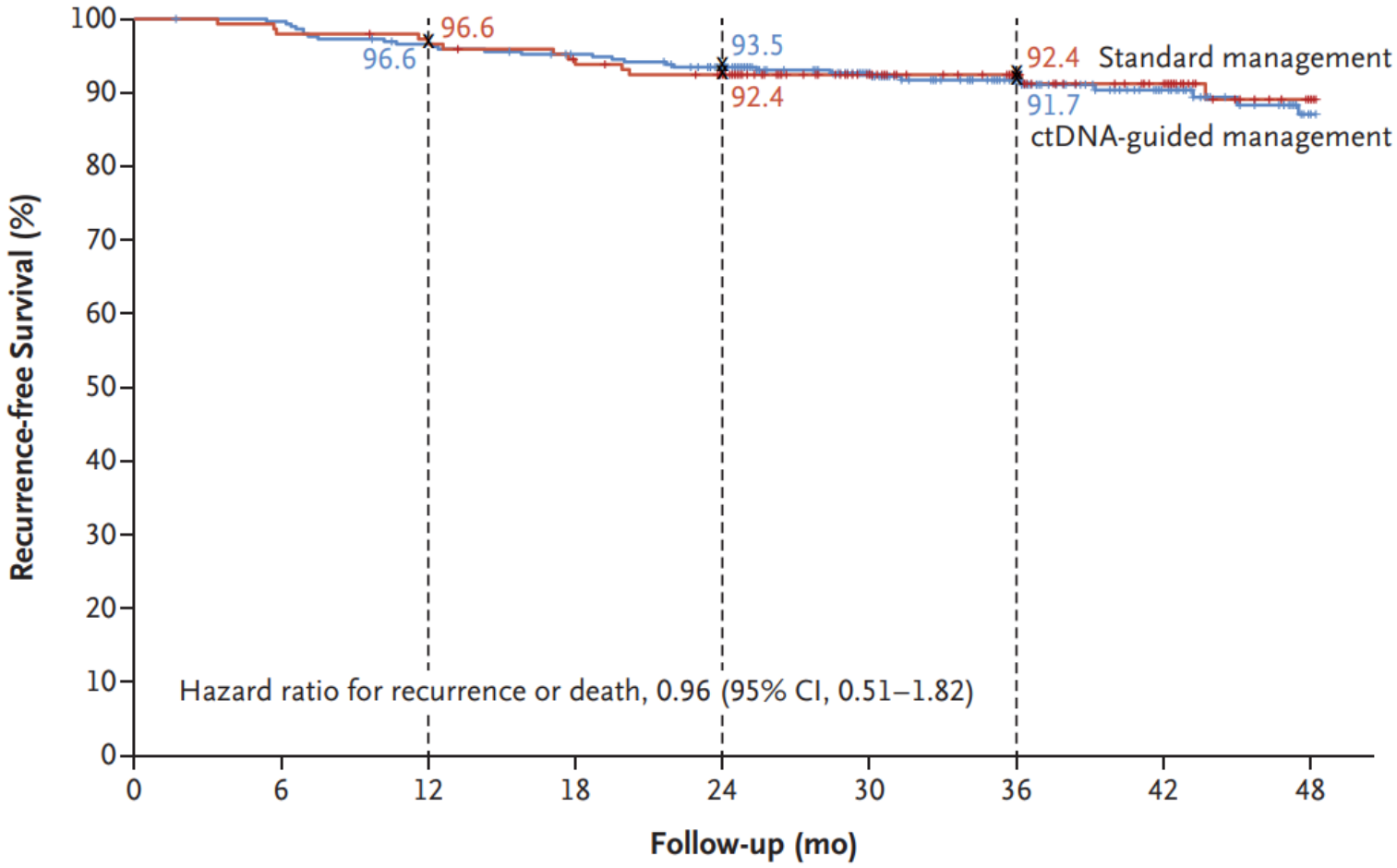
Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

Number at risk

W/ ACT	214	211	79	0
W/O ACT	317	309	117	0

HR was adjusted by age, performance status, pStage, and MSI status that are imbalanced between two groups.
ACT, adjuvant chemotherapy; DFS, disease-free survival; HR, hazard ratio; CI, confidential interval.
DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

B Kaplan–Meier Estimates of Recurrence-free Survival

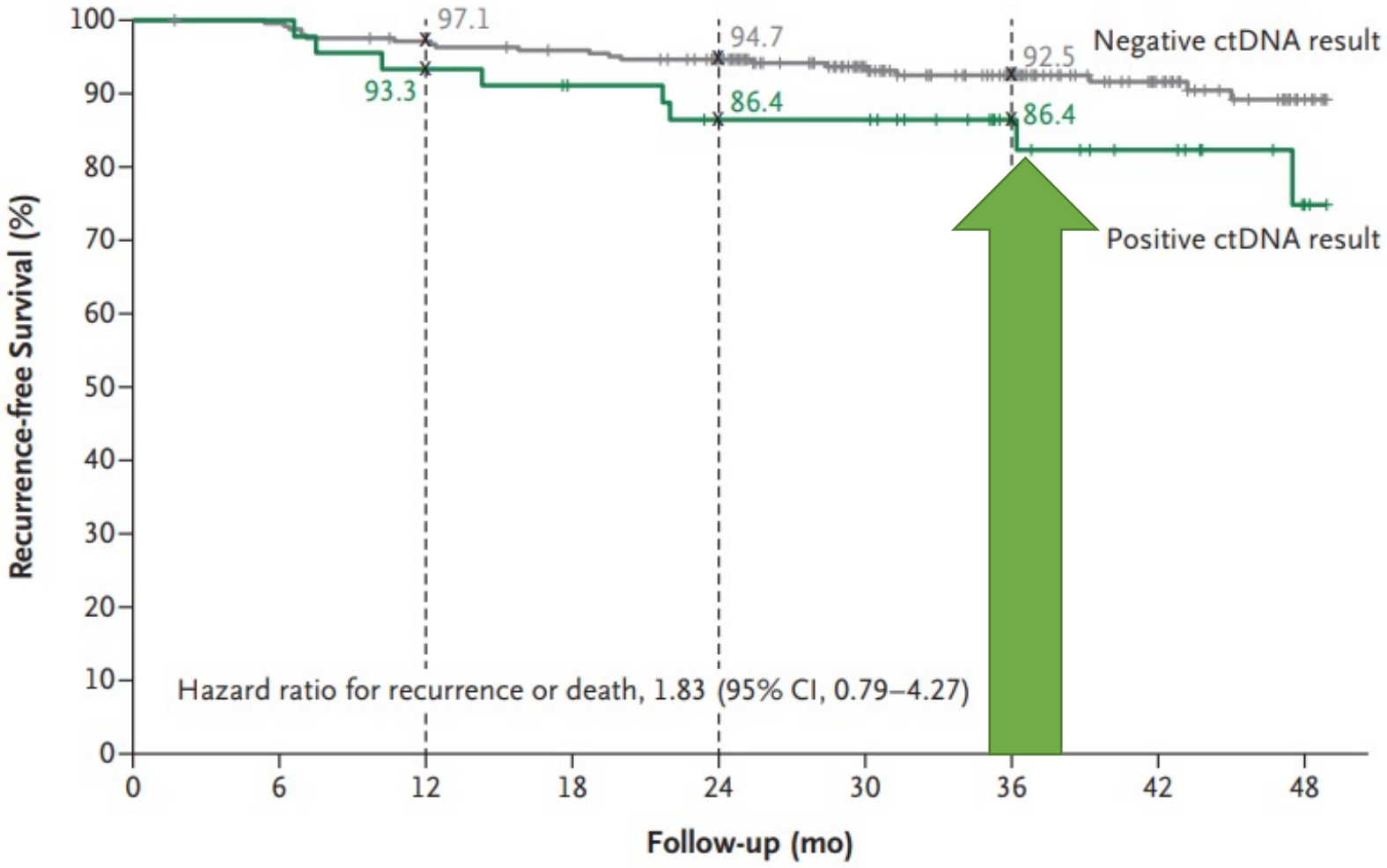


No. at Risk

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

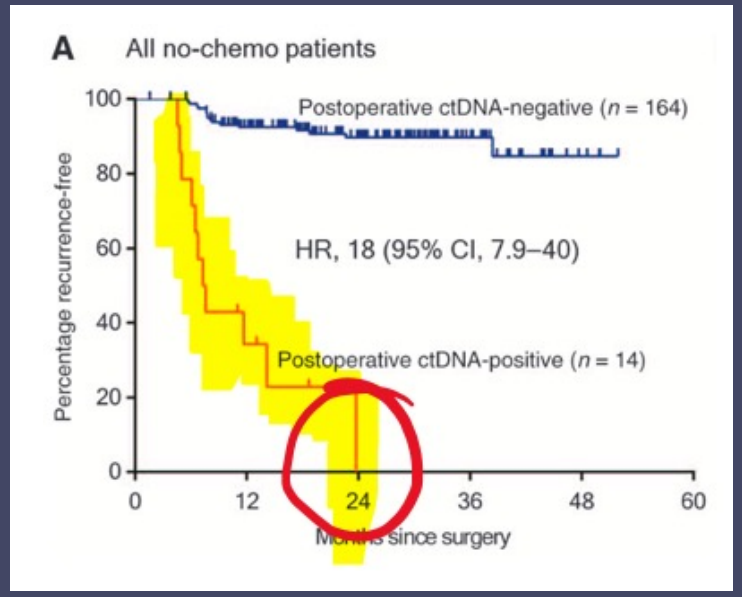
Tie et al. June 16, 2022
N Engl J Med 2022; 386:2261-2272

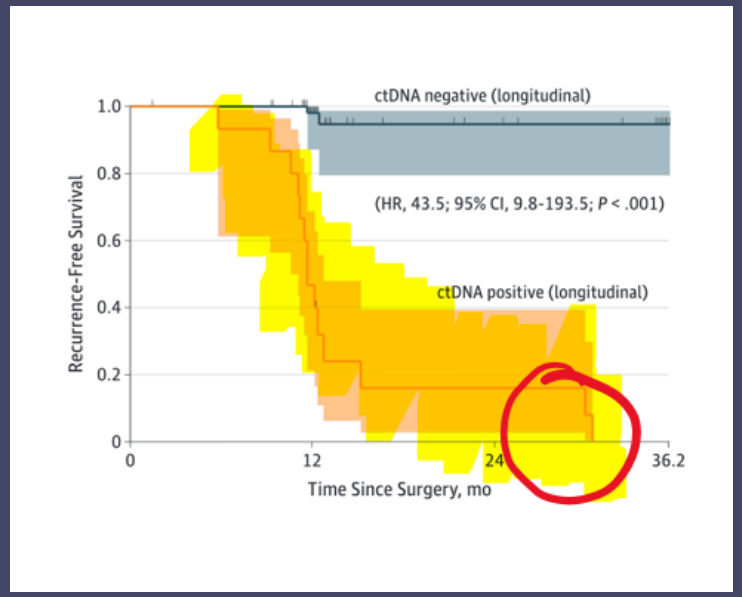


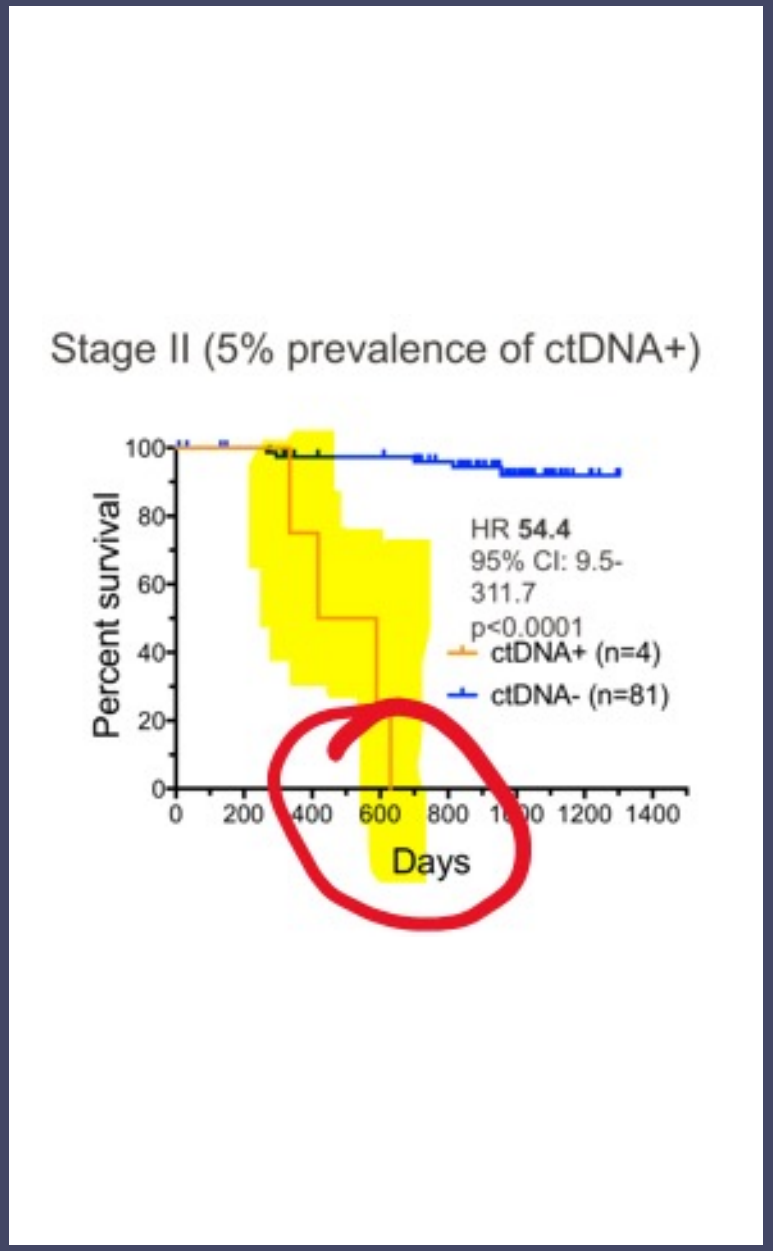
The NEW ENGLAND JOURNAL of MEDICINE

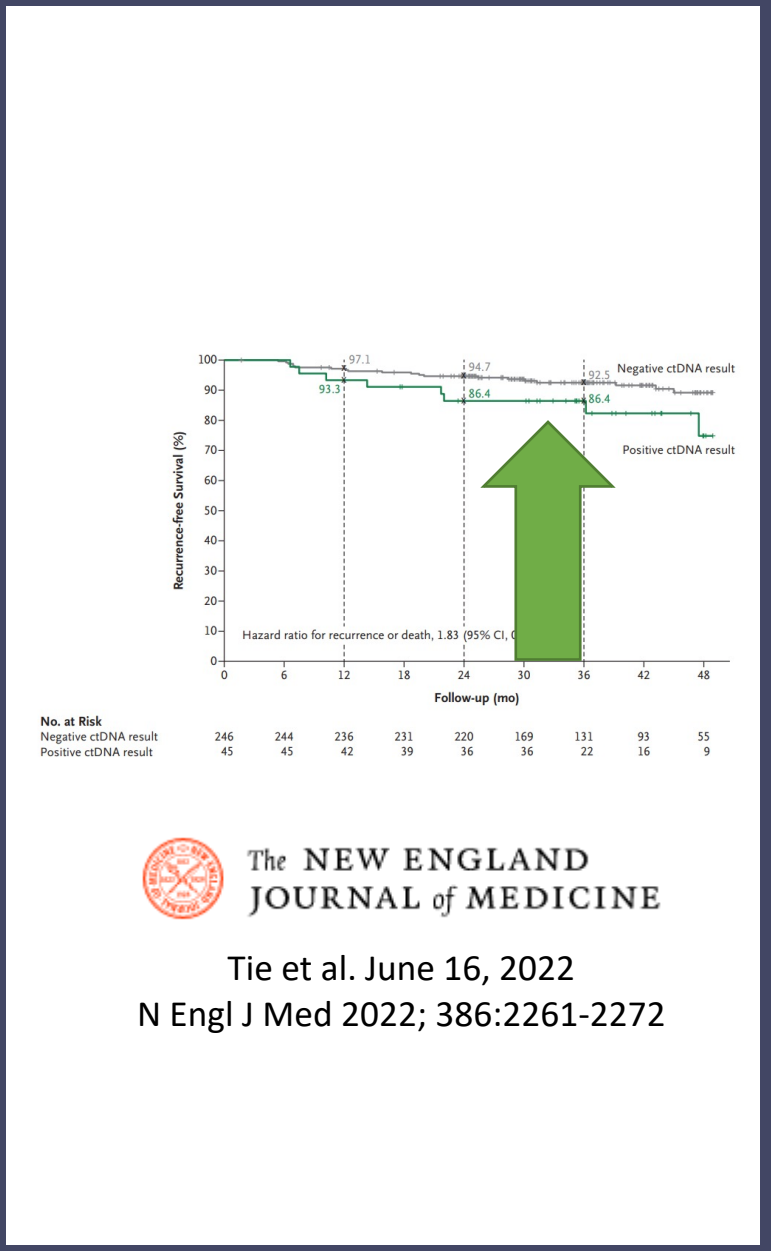
Tie et al. June 16, 2022
N Engl J Med 2022; 386:2261-2272

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







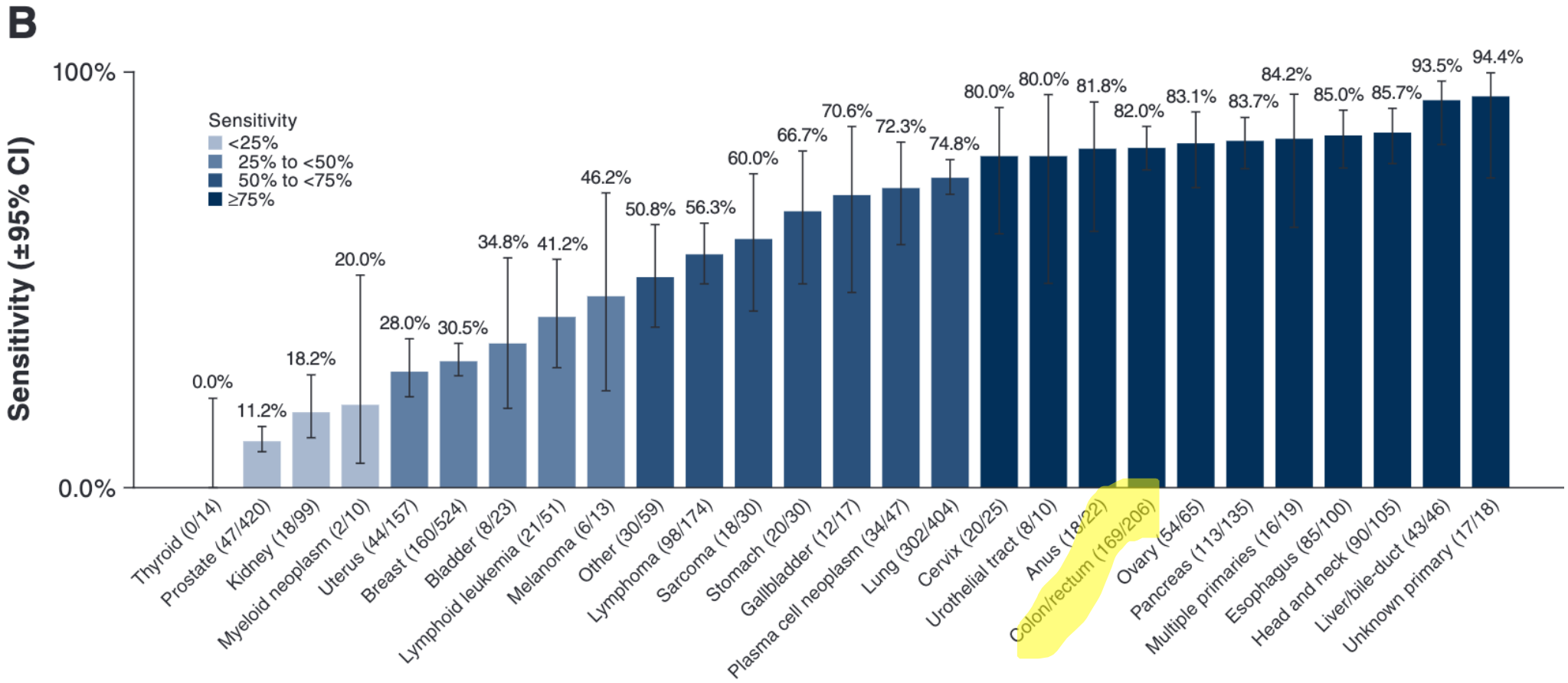


The NEW ENGLAND JOURNAL of MEDICINE

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

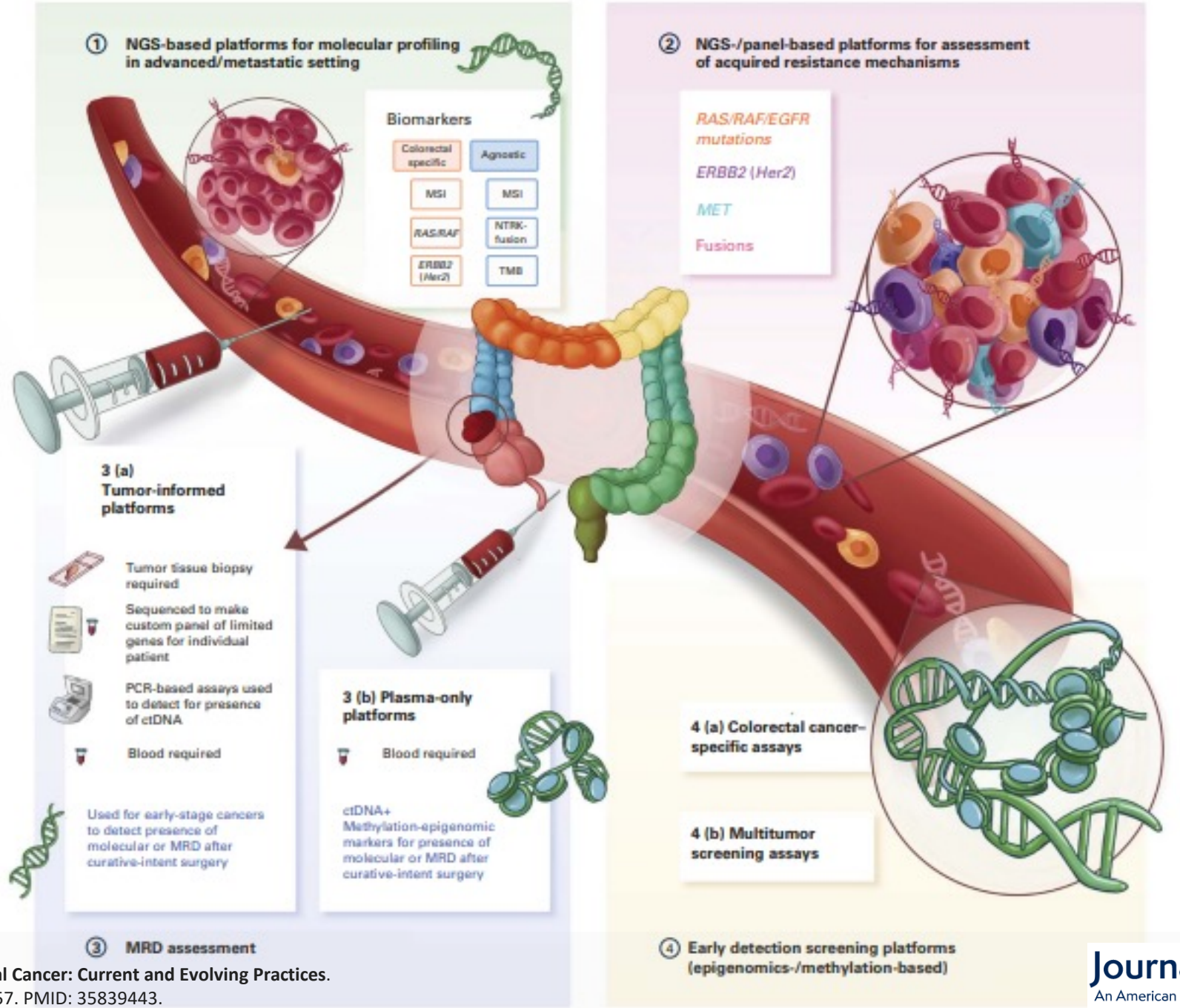
Summary/Future Directions

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*

Liquid Biopsies (ctDNA) in Clinic for Colorectal Cancer



Malla M, Loree JM, Kasi PM, Parikh AR.
Using Circulating Tumor DNA in Colorectal Cancer: Current and Evolving Practices.
J Clin Oncol. 2022 Aug 20;40(24):2846-2857. PMID: 35839443.

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How I Use Liquid Biopsy for GI Cancers in 2023

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