CIRCULATING TUMOR DNA TO GUIDE ADJUVANT THERAPY IN COLORECTAL CANCER IS READY FOR PRIME TIME: *AGREE*

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Designated
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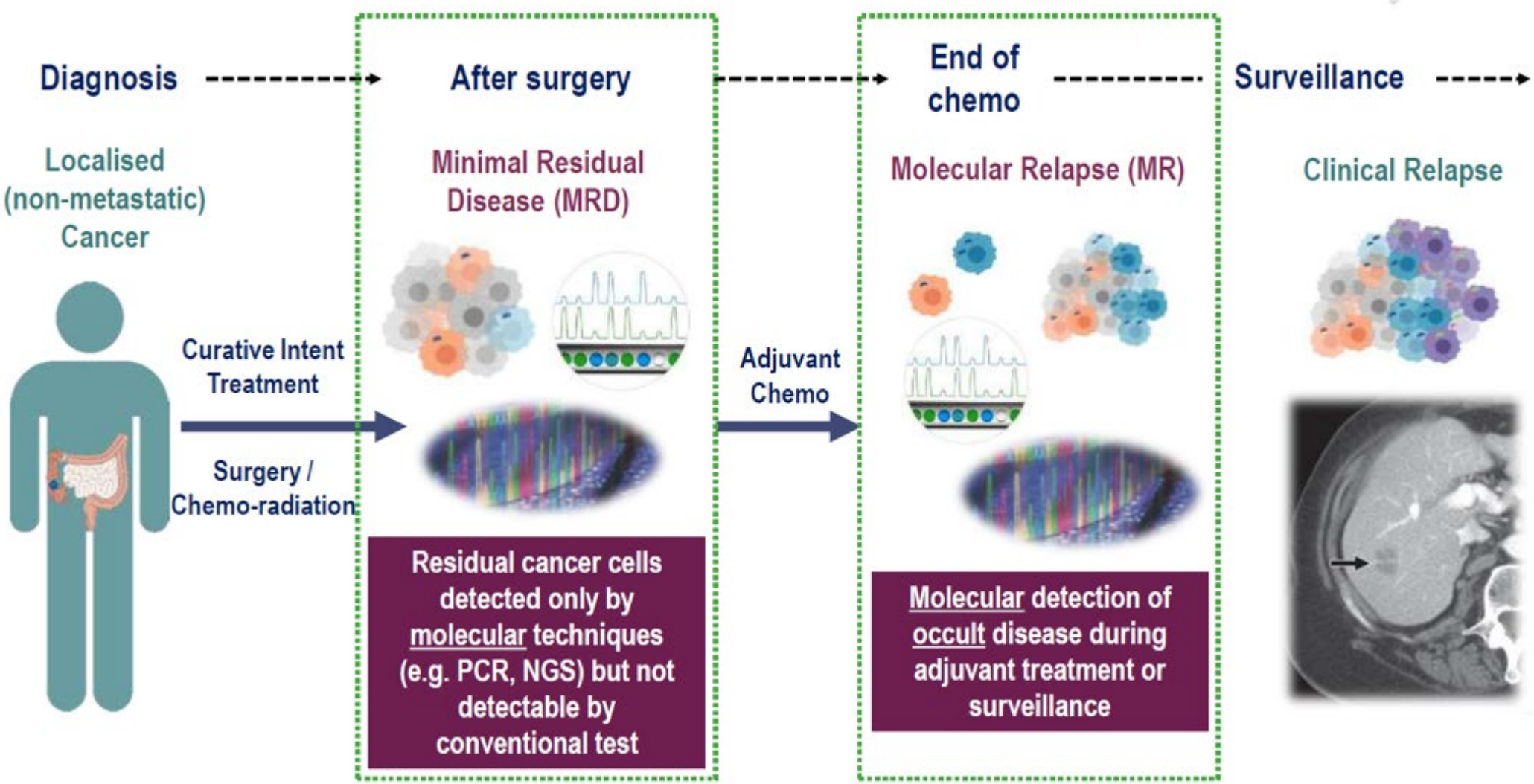
Disclosures

- Guardant, Novartis.

Minimal Residual Disease/Molecular Relapse- Definitions



Current challenges in adjuvant treatment

- **Stage-based approach is imprecise**
  - Undertreating stage II
  - Overtreating stage III
- **Lack of better treatments than FOLFOX**
  - Irinotecan
  - Bevacizumab
  - Cetuximab

- **Adjuvant trials are inefficient**
  - Lack of real-time marker to assess effectiveness of adjuvant therapy
  - Requires large sample size, long follow-up
  - Current trial infrastructure not suited for rapidly evolving novel therapies

Personalizing Adjuvant Therapy Biomarker

Localised (non-metastatic) Cancer

Definitive Rx (e.g. surgery)

Prognostic Enrichment

(MRD Detection)

Who Needs Adjuvant Rx?

Adjuvant Treatment

Early Readout of Rx Efficacy

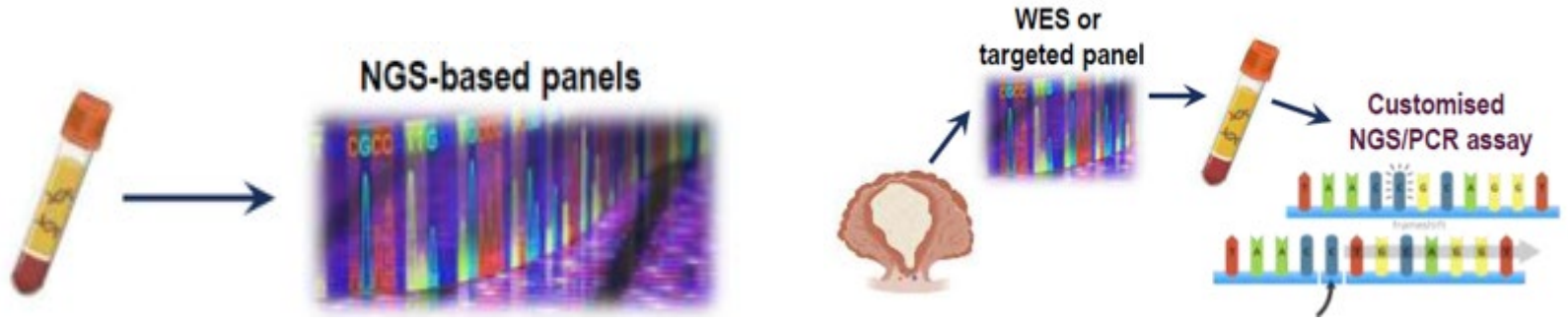
(MR Monitoring)

Is a Given Treatment Effective?

If not

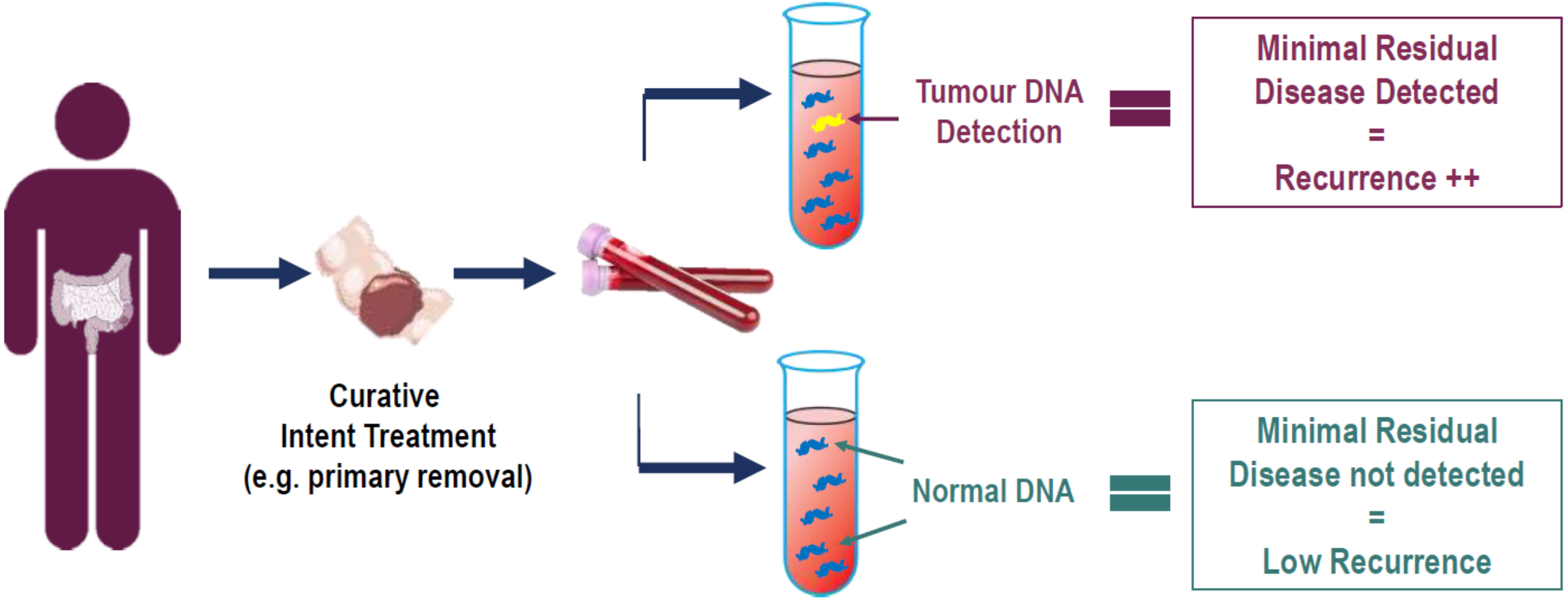
Role of "2nd line" adjuvant treatment?

MRD- Two approaches to ctDNA analysis

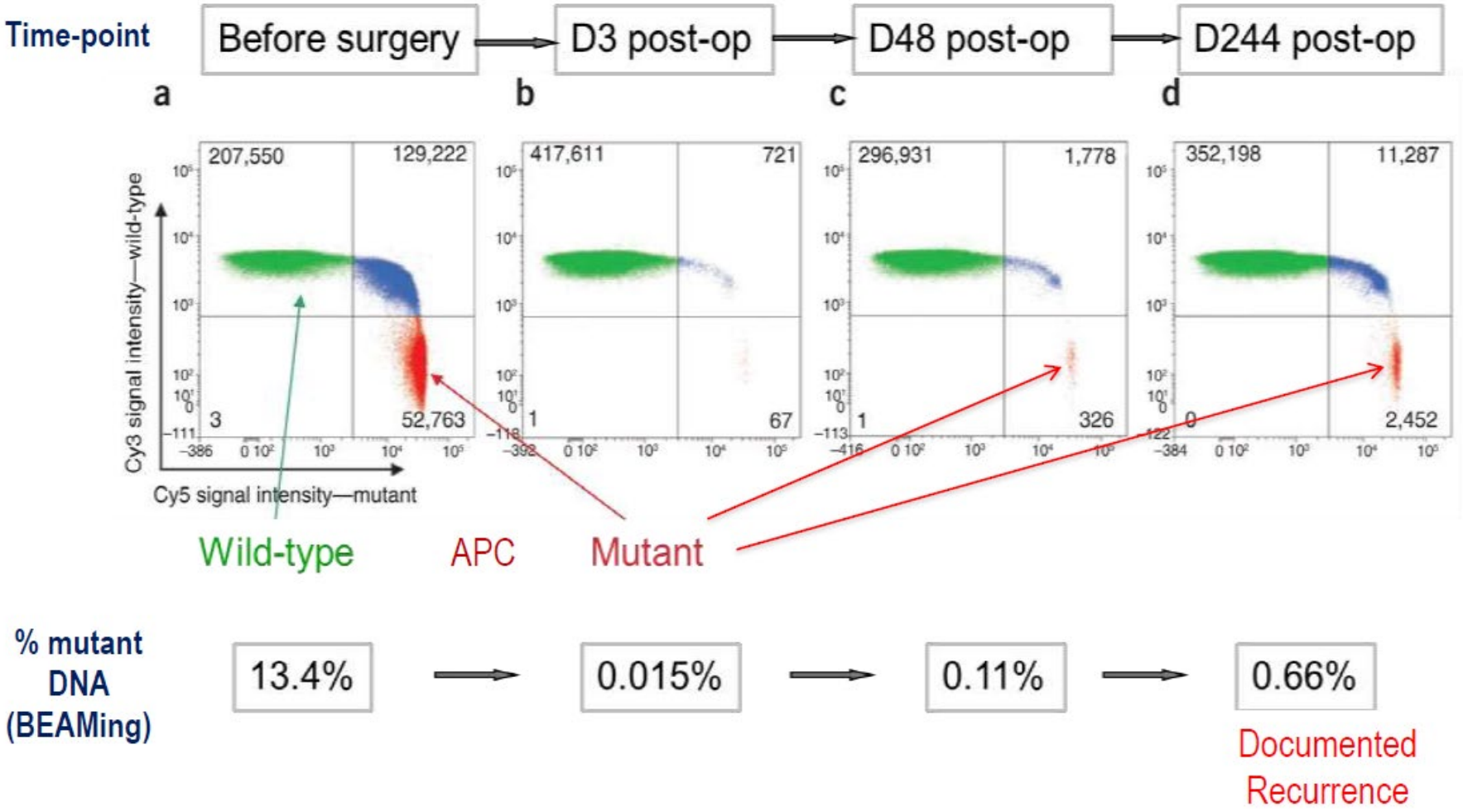


	Tumor-agnostic	Tumor-informed
Method	Detect mutation de novo from plasma (one assay for all)	Identify mutations in tumor tissue->track mutations in plasma (customized)
Key Advantage	Does not require tissue	Higher sensitivity
Key Disadvantage	Lower sensitivity due to multiple hypothesis testing	Requires tissue

ctDNA redefines recurrence risk assessment

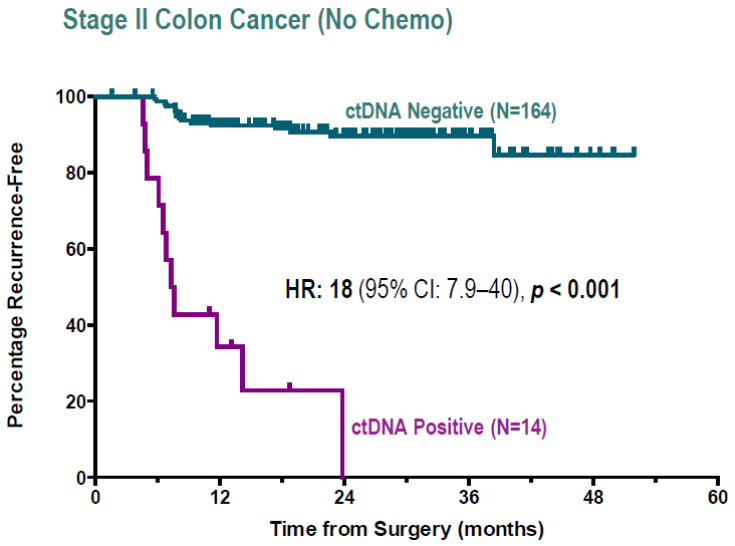


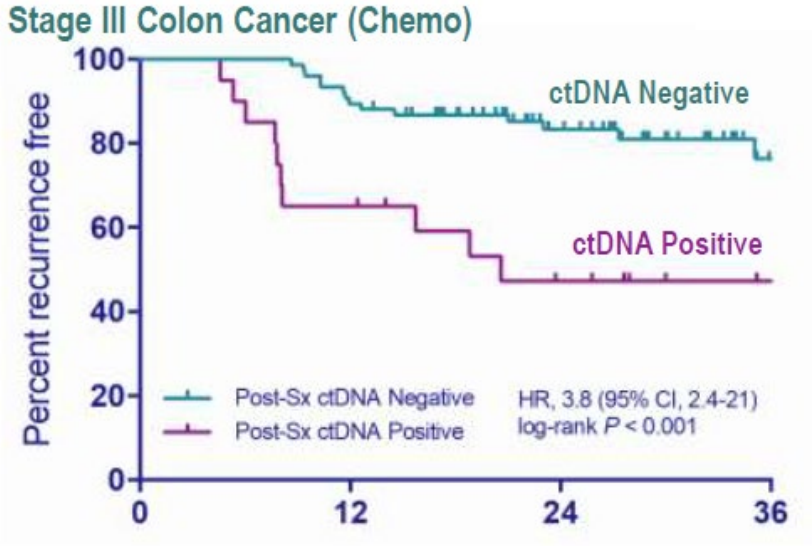
ctDNA reflects tumor burden in CRC

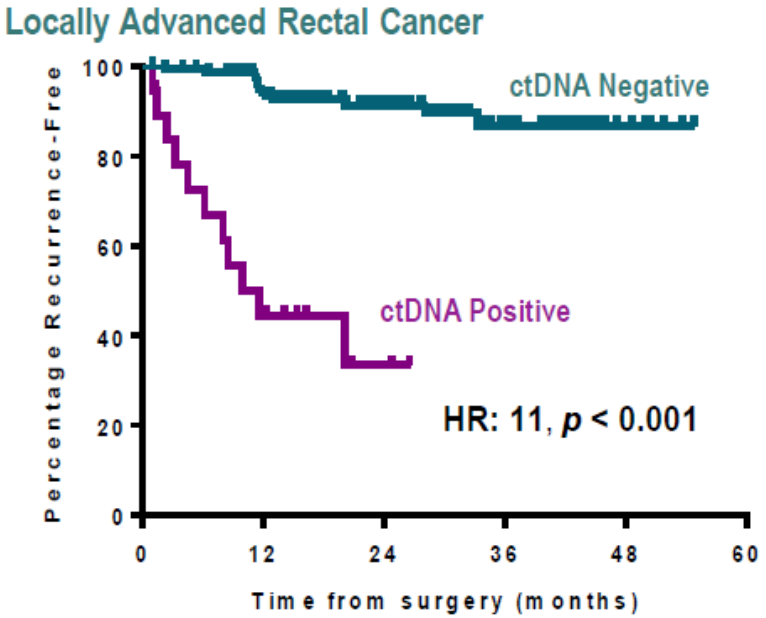


F Diehl et al. Nature Medicine 2008;14(9):985-990.

Post-op ctDNA Detection Predicts For Recurrence



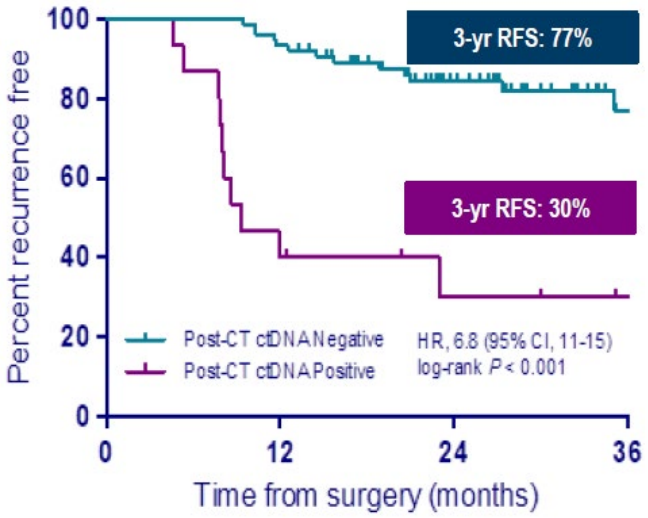




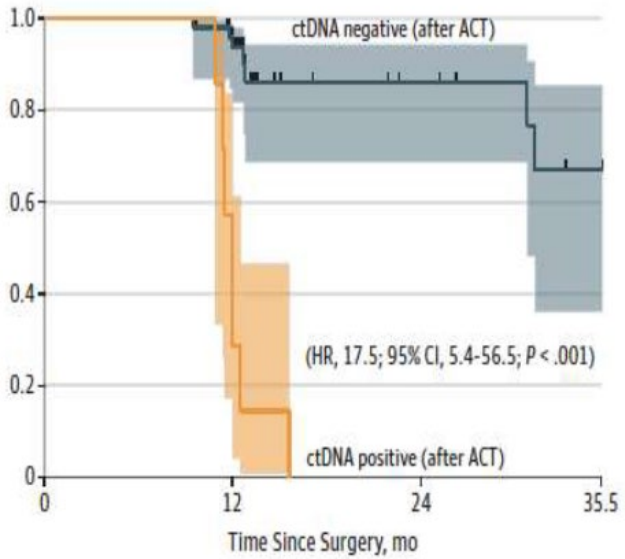
Tie J et al. Sci Transl Med. 2016;8(346):346ra92; Tie J et al. JAMA Oncology, 2019; Tie J et al. Gut, 2019;69(4):663.671.

Post-treatment ctDNA is a surrogate for treatment efficacy

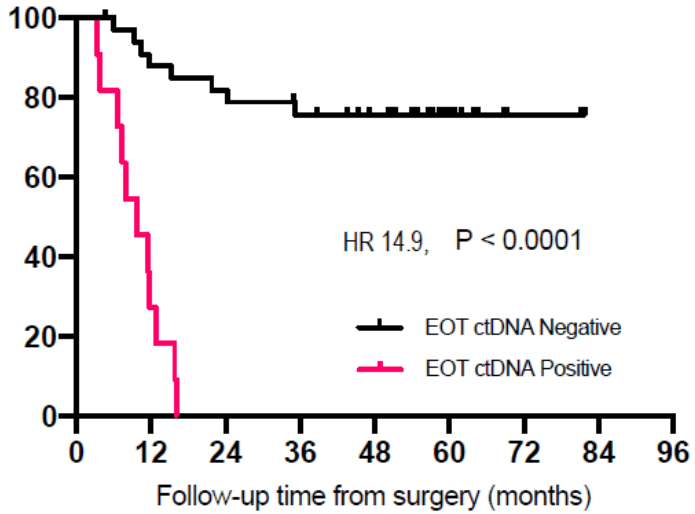
Stage III CC



Stage II-III CC

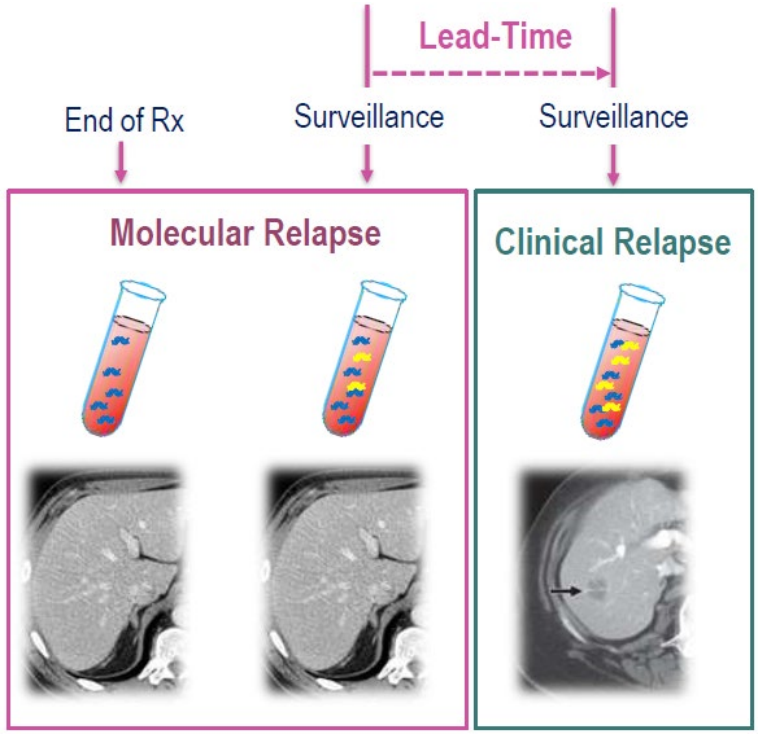


Resected CRC liver mets



Tie J, et al. JAMA Oncol 2019;5(12):1710-1717; Reinert T, et al. JAMA Oncol 2019;5(8):1124-1131; Tie J, et al. PLoS Med 2021;18(5):e1003620.

ctDNA during surveillance- Lead-time to clinical recurrence

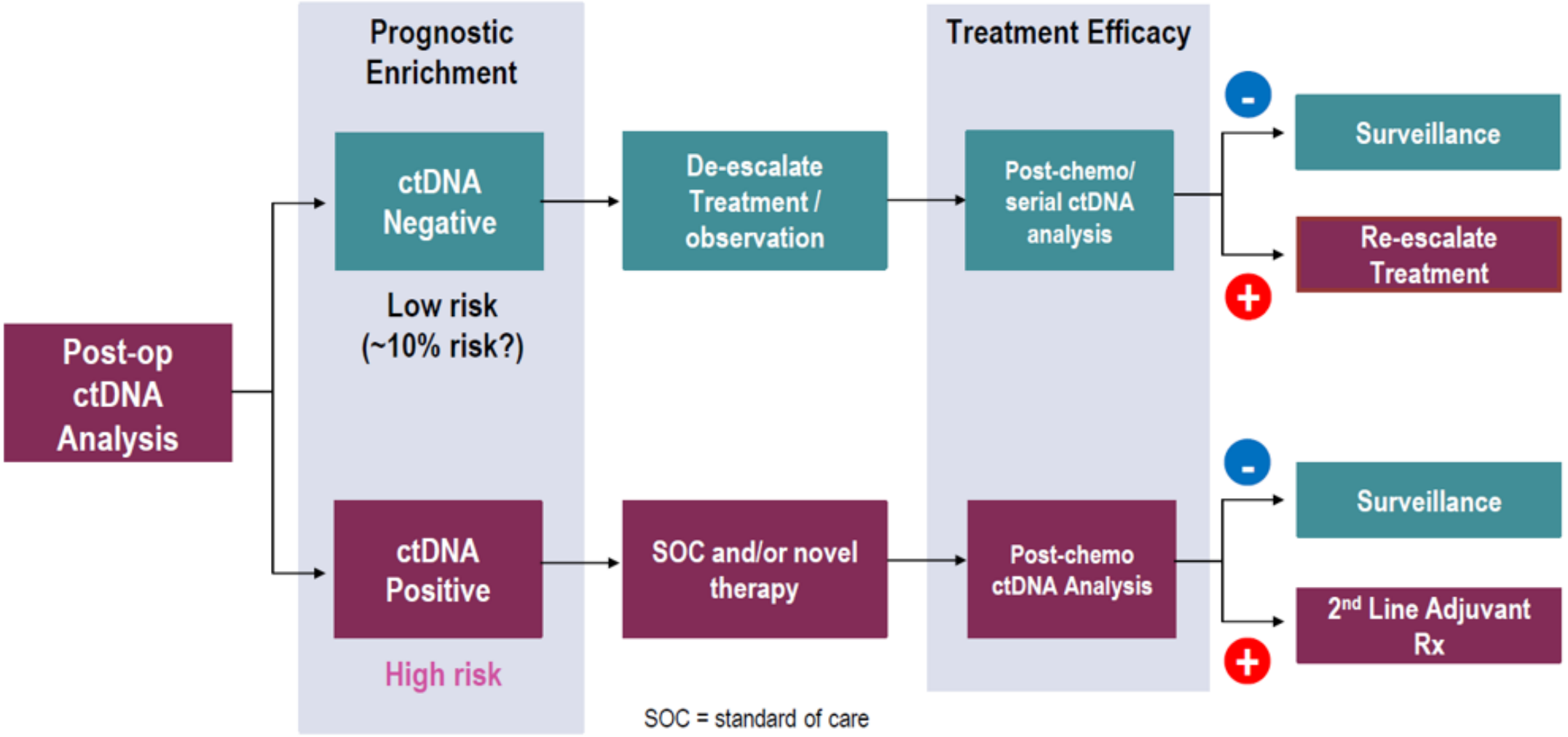


- **Lead-time=** Time between first detection of ctDNA from the end of definitive treatment and clinically detectable recurrence
- **Affected by:**
  - frequency of ctDNA testing and imaging
  - sensitivity of ctDNA assay and imaging modality
  - tumor biology / site of relapse
- **Increasing ctDNA detection rate with increasing time after surgery**

Study	Frequency of Testing		Lead-Time median (range)
	ctDNA	CT scan	
Tie J, *et al.* (SII)	Q3M	Q6M	5.6M (IQR 2.7-9.3)
Tie J, *et al.* (SIII)	Q3M	1M + Q12M	1.7M (0.3-15.7)
Tarazona N, *et al.*	Q4M	Q6M	11.5M (3-18)
Chen G, *et al.*	Q3M	Q12M	5.1M (not reported)
Wang Y, *et al.*	Q3-6M	not reported	4M (2-31)
Henriksen TV, *et al.*	Q3M	12M + 36M	8M (0.56-21.6)

Sci Transl Med 2016;8(346):346ra92; JAMA Oncology 2019;5(12):1710-1717; Ann Oncol 2019;30(11):1804–1812; J Hematol Oncol 2021;14:80; JAMA Oncol 2019;5(8):1118-1123; JCO 2021;39:3_suppl,11-11.

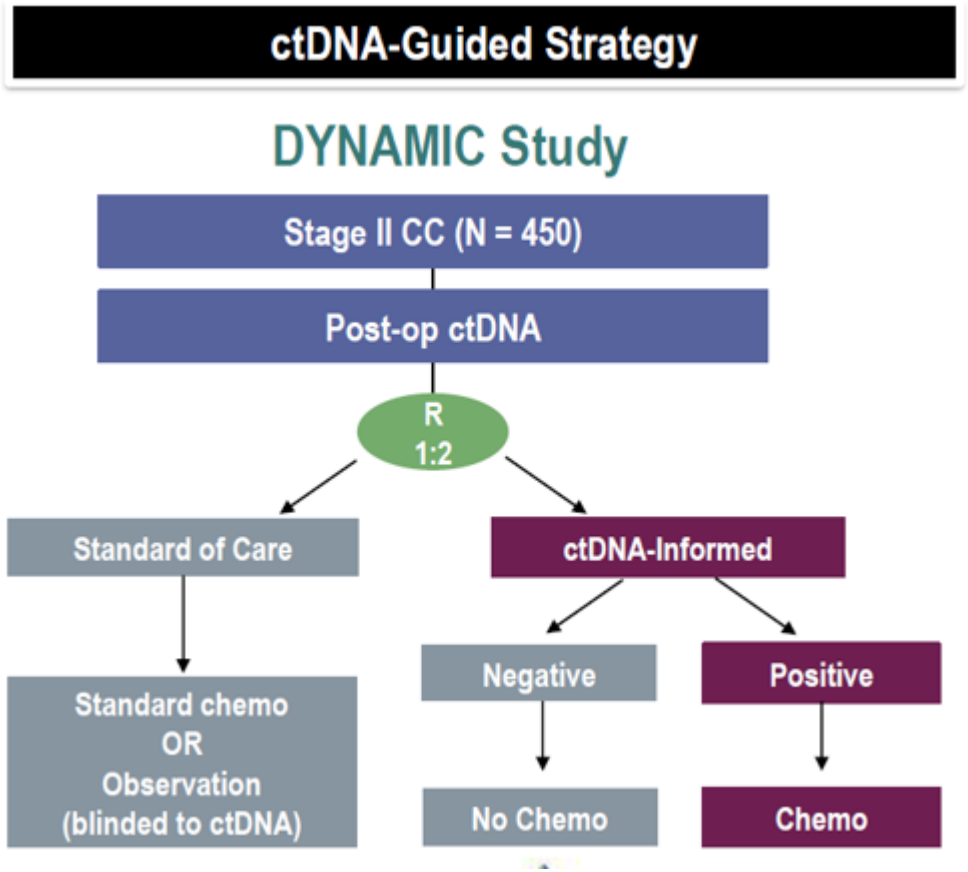
ctDNA-guided approach to adjuvant treatment

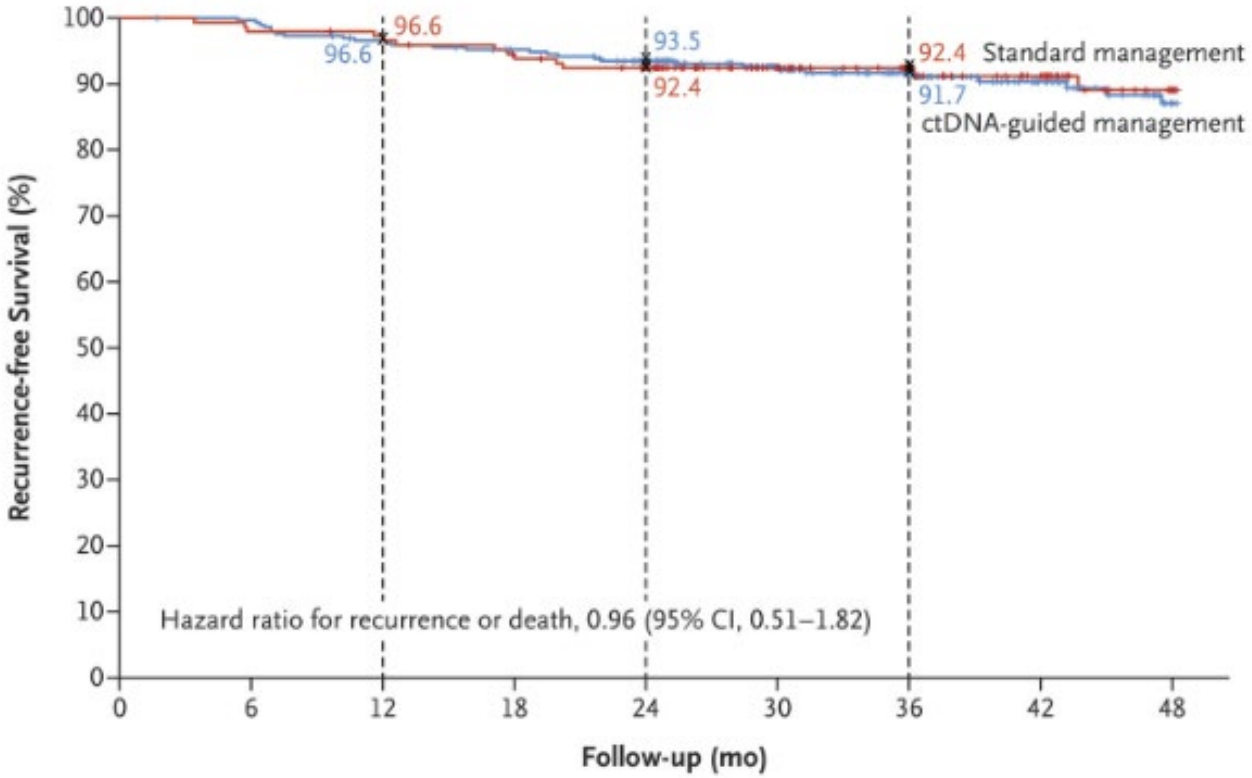


ctDNA-informed trials for colon cancer

Stage 1	Stage 2	Stage 3	Stage 4
BESPOKE	BESPOKE	BESPOKE	BESPOKE
	COBRA		
	DYNAMIC	DYNAMIC-III	
	CIRCULATE-PRODIGE 70		
	CIRCULATE-JAPAN/US	CIRCULATE-JAPAN/US	CIRCULATE-JAPAN
		ACT3	

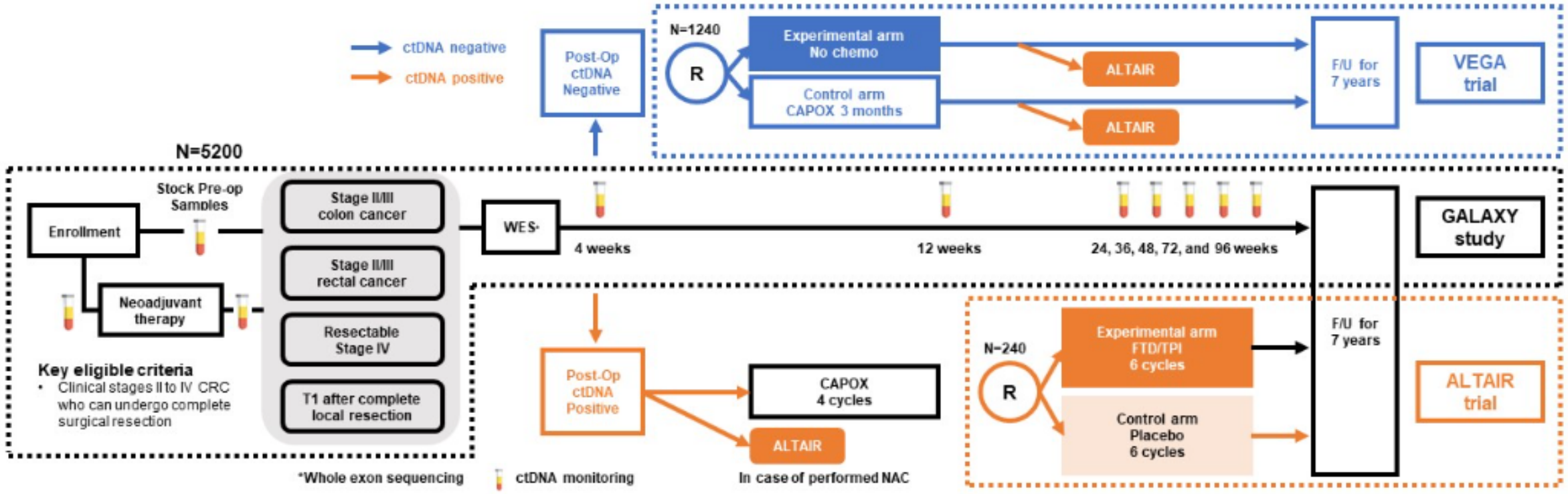
DYNAMIC trial





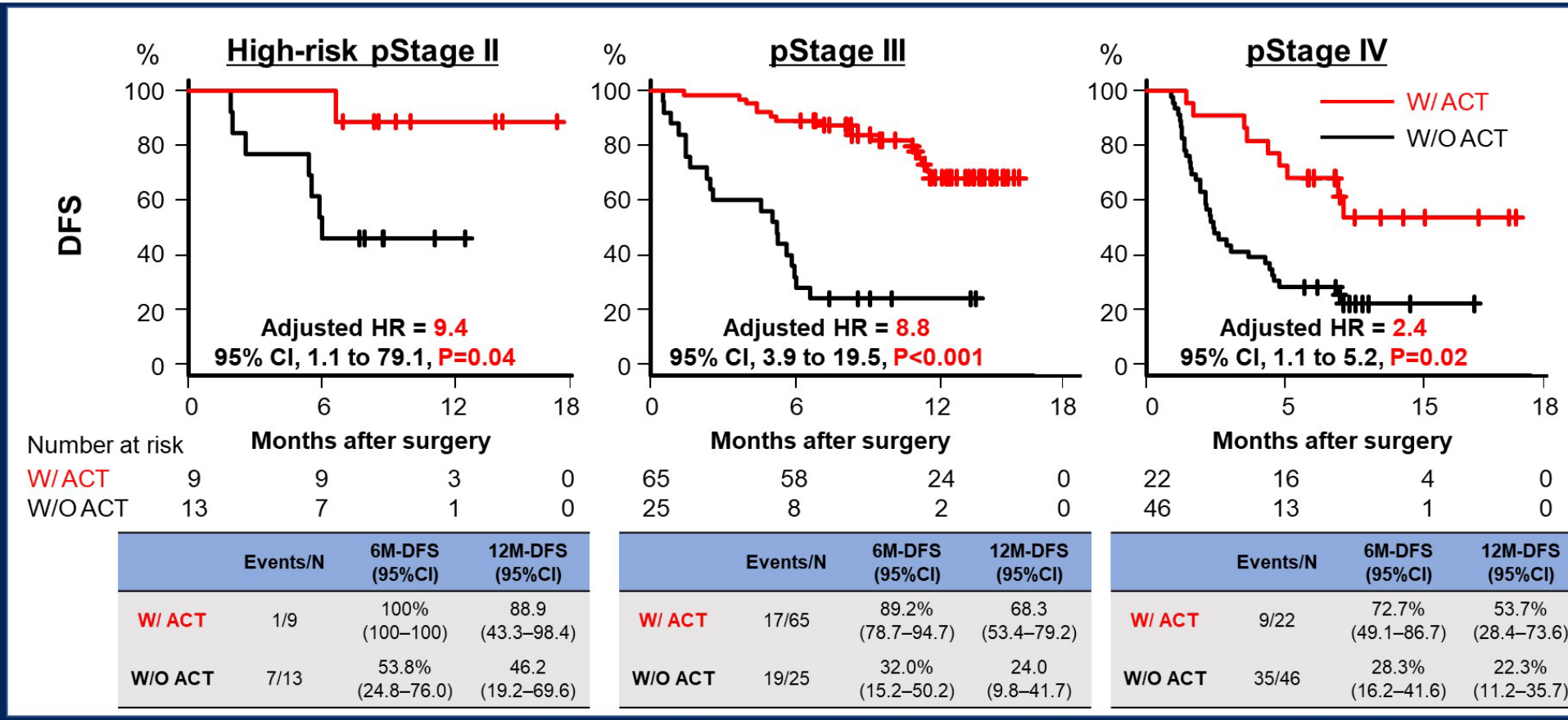
Tie J et al. N Engl J Med. 2022 Jun 16;386(24):2261-2272.

CIRCULATE-Japan



GALAXY-significant benefit from adjuvant chemo for MRD+

DFS by pStage in post-op-4w ctDNA positive population



	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	1/9	100% (100–100)	88.9 (43.3–98.4)
W/O ACT	7/13	53.8% (24.8–76.0)	46.2 (19.2–69.6)

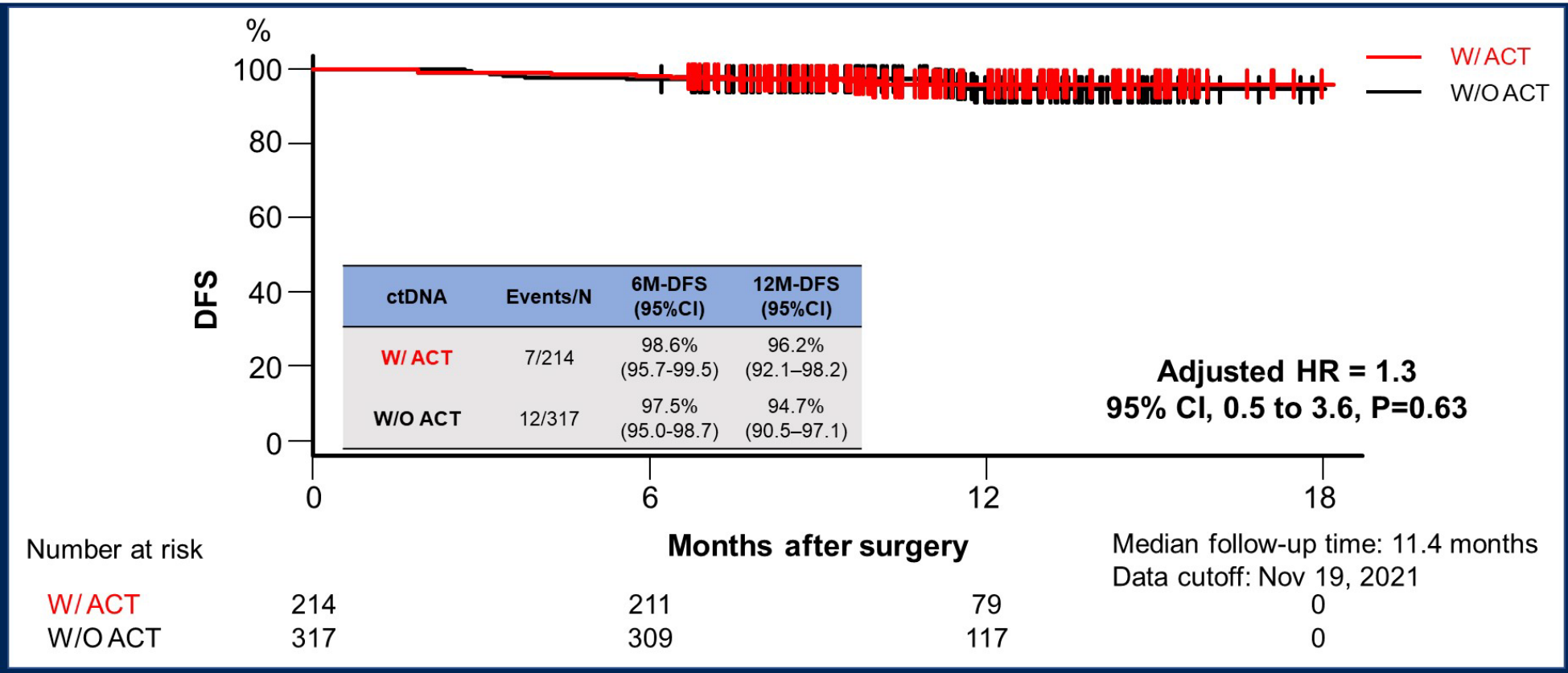
	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	17/65	89.2% (78.7–94.7)	68.3 (53.4–79.2)
W/O ACT	19/25	32.0% (15.2–50.2)	24.0 (9.8–41.7)

	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	9/22	72.7% (49.1–86.7)	53.7% (28.4–73.6)
W/O ACT	35/46	28.3% (16.2–41.6)	22.3% (11.2–35.7)

HR was adjusted by sex, and performance status. 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.

GALAXY-no benefit from adj chemo for MRD-

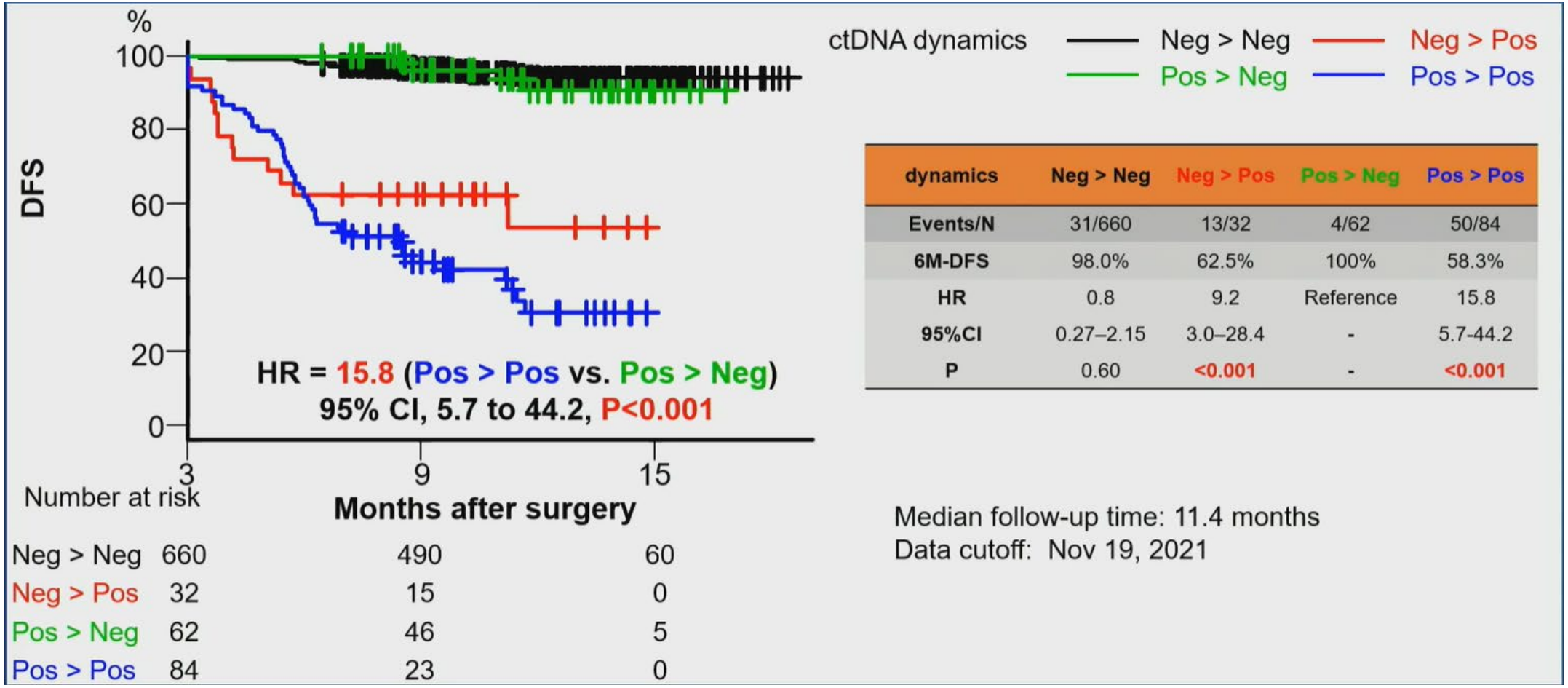
DFS by ACT in post-op-4w ctDNA negative population (High-risk pStage II-III)



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)

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.

GALAXY - DFS by ctDNA dynamic from postop w4 to w12



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

Conclusion

ctDNA is ready for prime time!