Controversies in Colon Cancer: ctDNA in the Adjuvant Therapy of Colon Cancer and in the Management of Oligometastases

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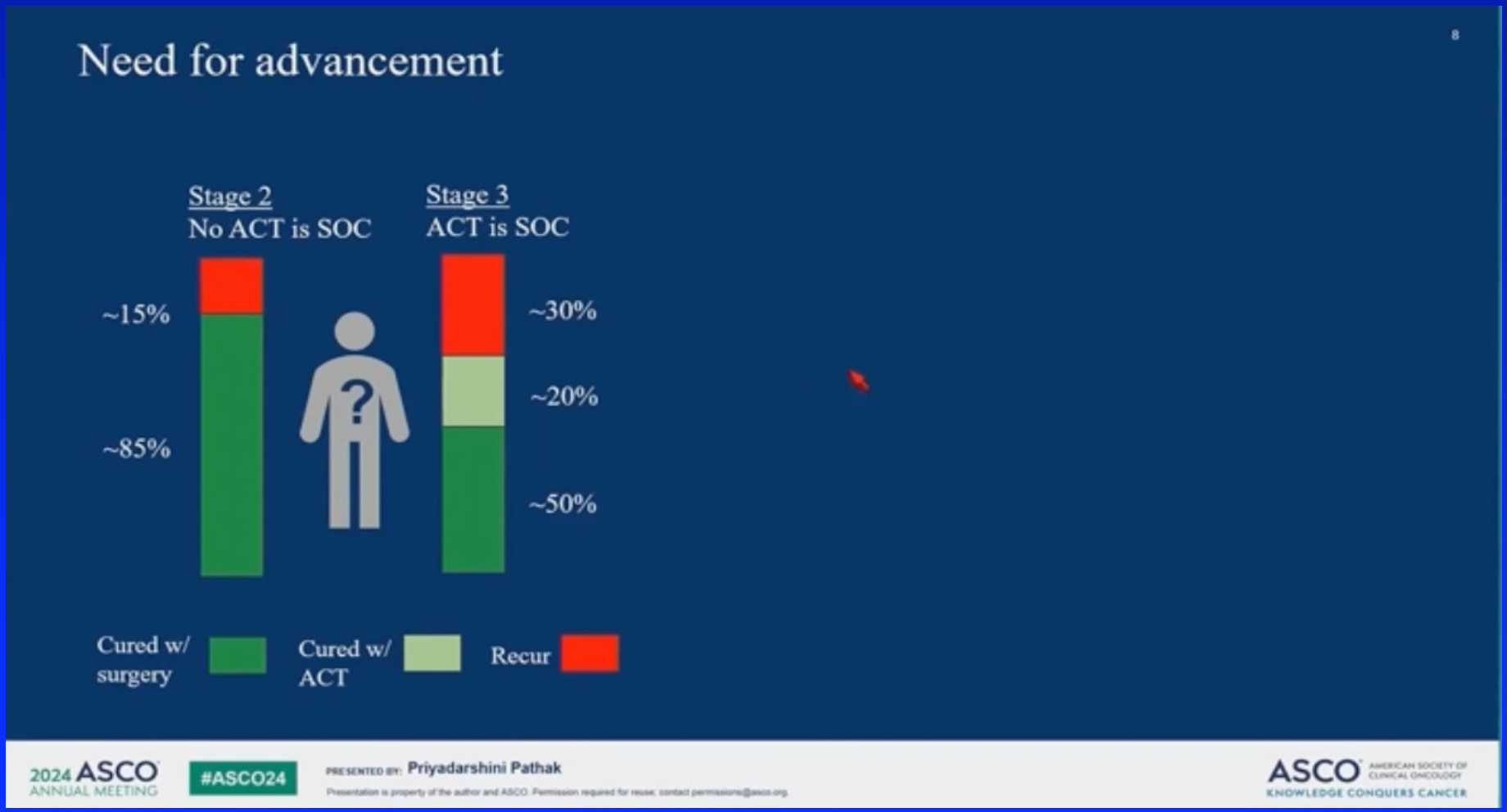
Need


Need for advancement
8
Stage 2
No ACT is SOC
Stage 3
ACT is SOC
~15%
~85%
~30%
~20%
~50%
Cured w/ surgery
Cured w/ ACT
Recur
2024 ASCO ANNUAL MEETING
#ASCO24
PRESENTED BY: Priyadarshini Pathak
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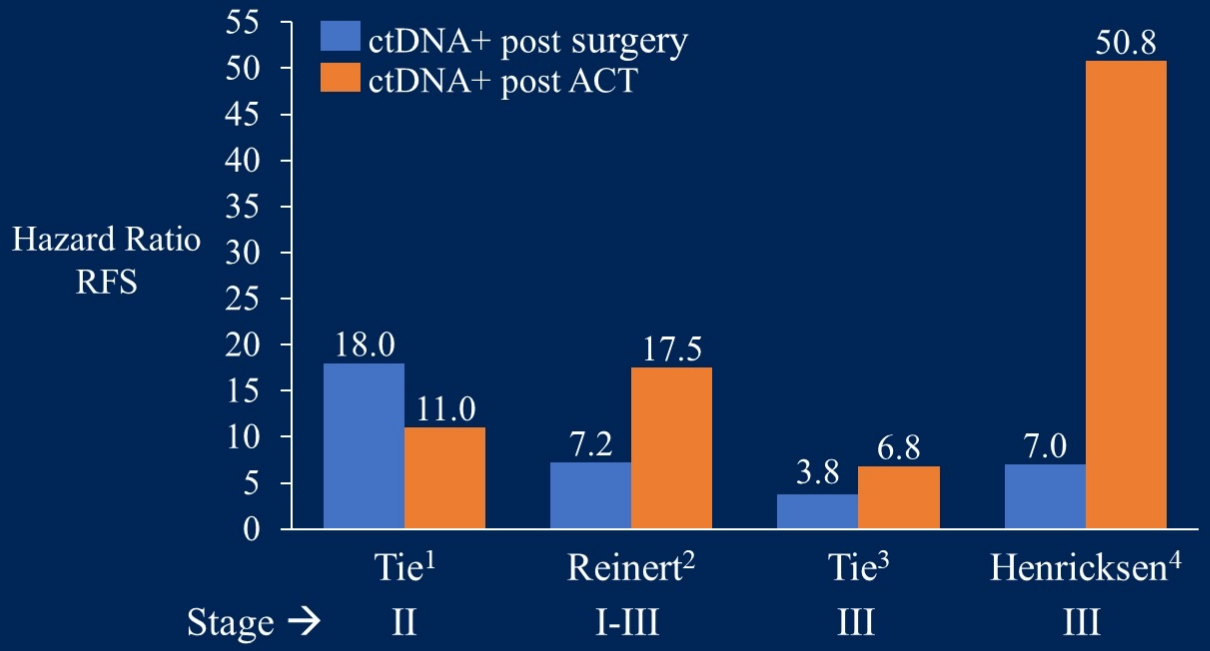
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

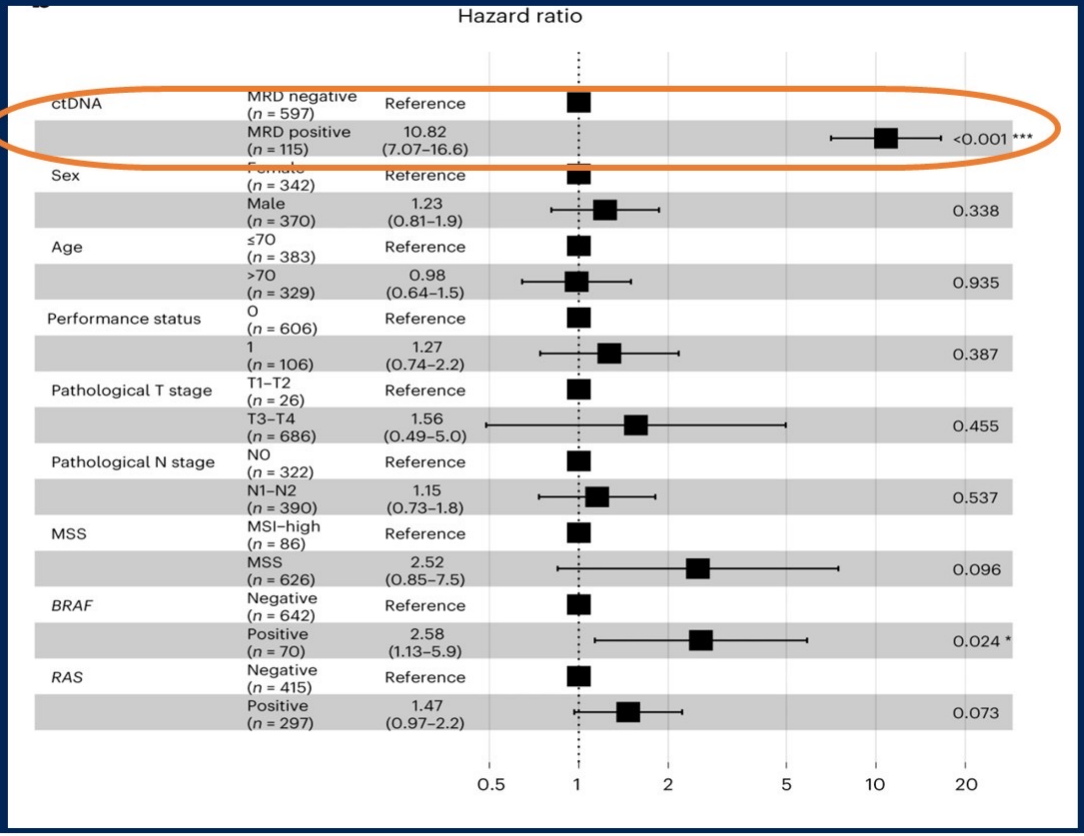
ctDNA is prognostic



~100% with + ctDNA post op develop clinical recurrence without any systemic therapy, usually within 2 years

1: Sci Transl Med. 2016
2: JAMA Oncol. 2019
3: JAMA Oncol. 2019
4: Clin Cancer Res. 2022

ctDNA is prognostic



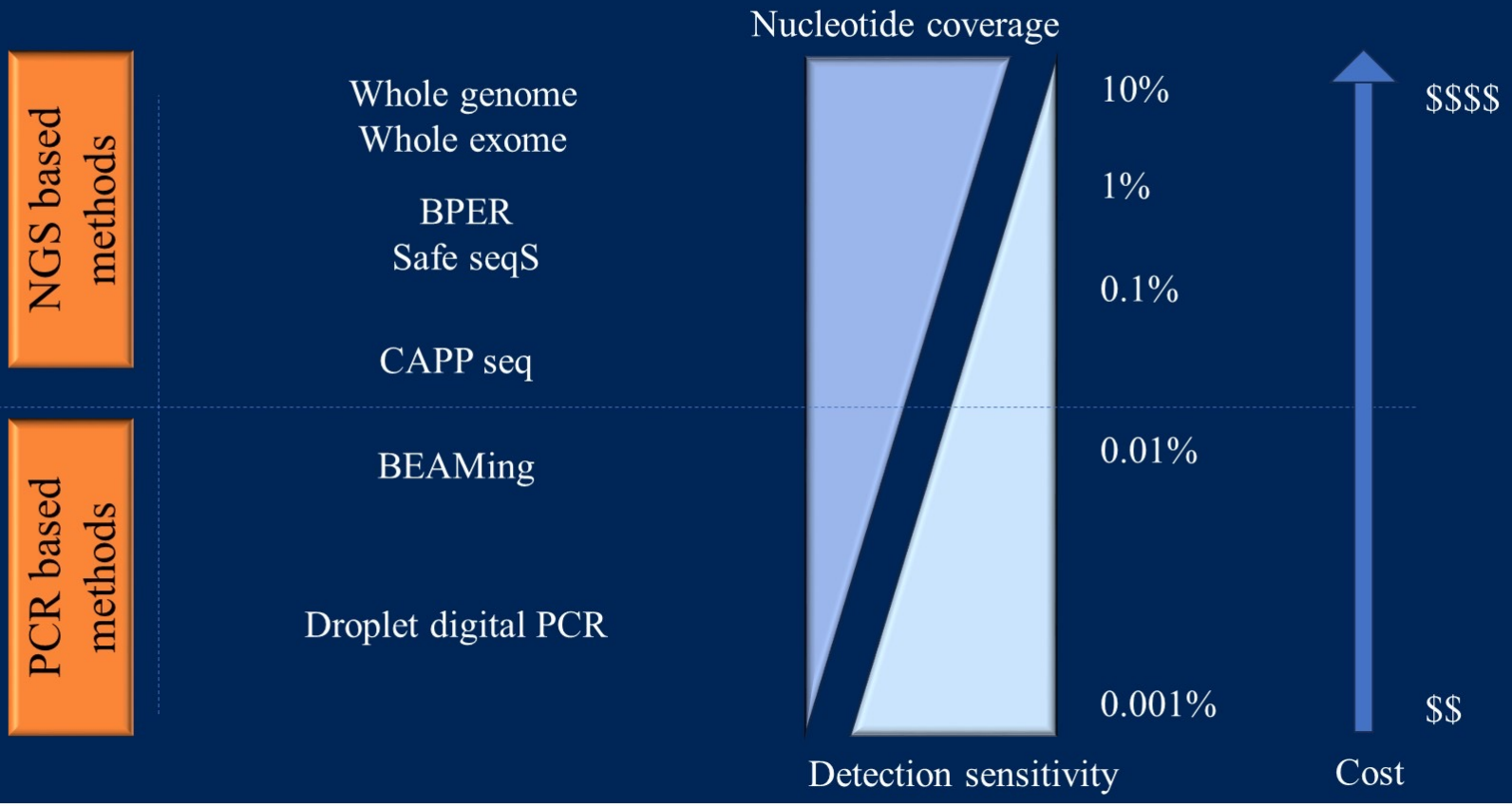
Multivariate analysis stage II–III:

Post op MRD + MOST significant prognostic factor associated with increased risk for recurrence

Kotani et al, Nature Medicine 2023

…but challenges are

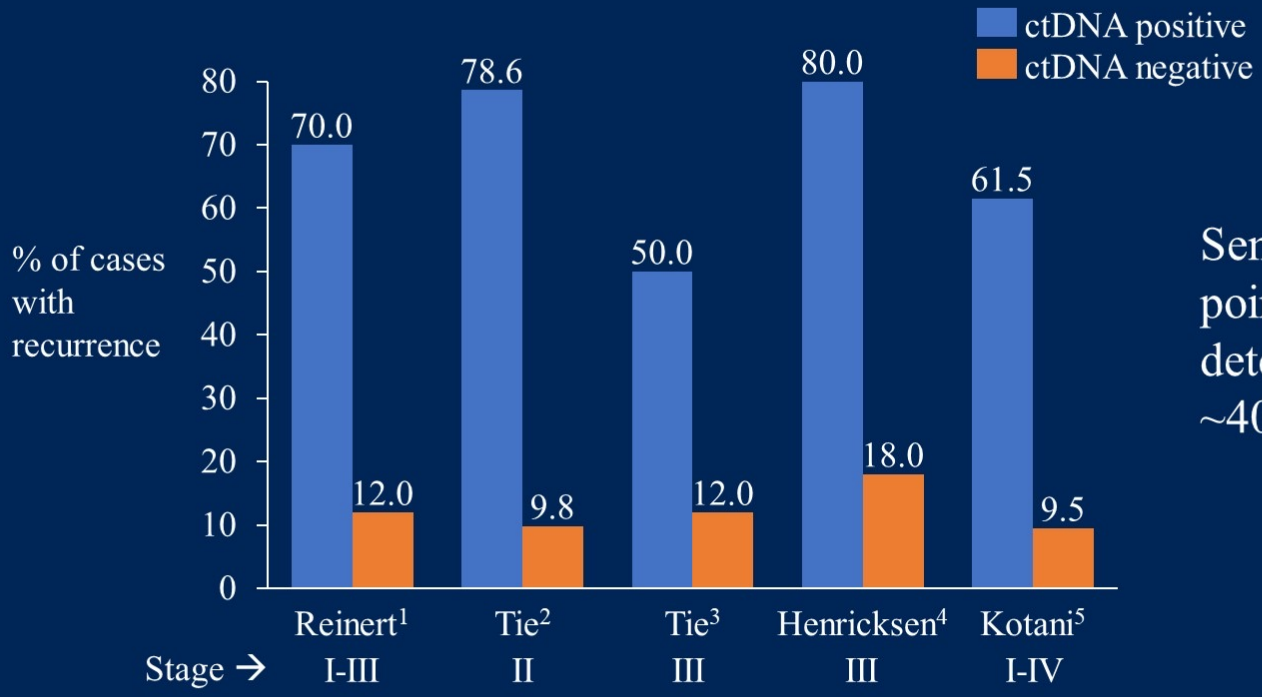
Methods for detection and analysis



ctDNA platforms

	Tumor informed (Bespoke)	Tumor agnostic
Method	Identify mutations in tumor tissue > track in plasma	Detect mutations de novo from plasma
Technique	Genomic (NGS, PCR)	Genomic + Epigenomic (E.g. methylation)
Turnaround time: 1st check	Initial 4-6 weeks	7-10 days
Turnaround time: 2nd check and beyond	7-10 days	7-10 days
Timing of collection post op	2-6 weeks	4 weeks
Detection of acquired mutations	No	Yes
Costs & logistics	Additional cost of tumor genotyping, need for adequate tumor cellularity in biopsy	Less invasive, plasma DNA costs only
Select examples	Signatera, Invitae/Archer, Haystack, RaDaR	Guardant Reveal, Tempus xM

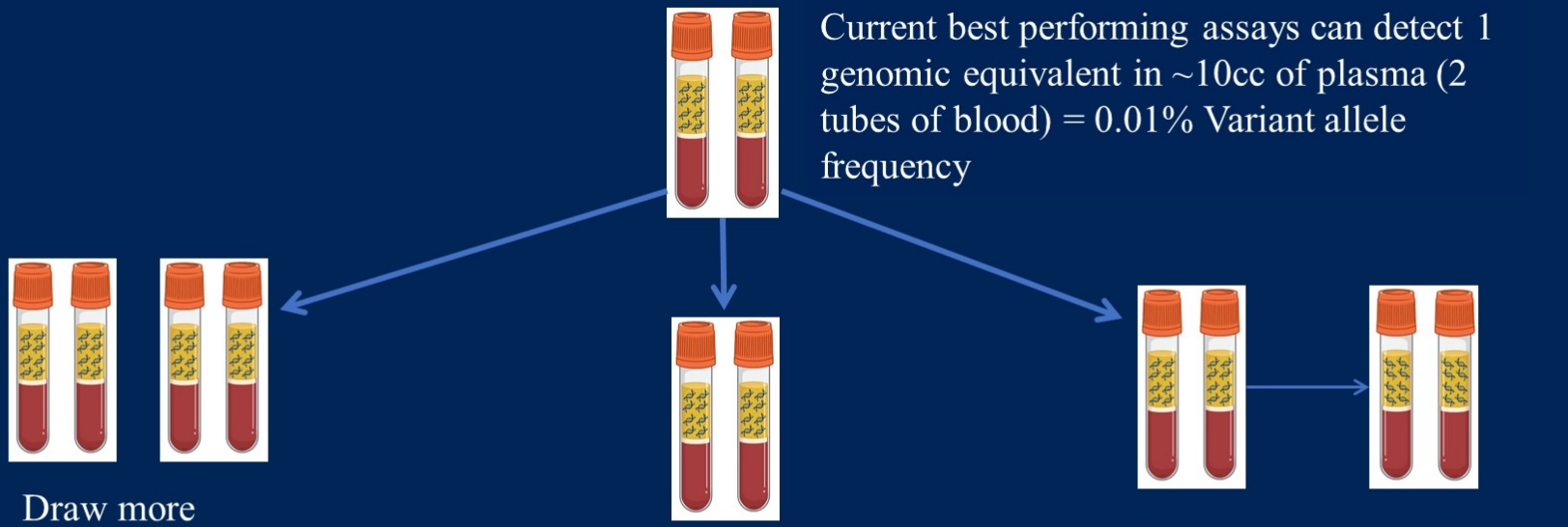
Sensitivity of ctDNA assays to detect recurrence is low



Sensitivity of single time point post op ctDNA to detect residual disease is ~40-50%

1: JAMA Oncol. 2019
2: Sci Transl Med. 2016
3: JAMA Oncol. 2019
4: Clin Cancer Res. 2022
5: Nat Med. 2023

How to improve sensitivity?



If risk of recurrence in ctDNA negative population can be lowered similar to Stage I (5y DFS ~95%), then de-escalation can be safely performed

ctDNA clearance with ACT is ~30%

Study	Stage	% ctDNA clearance with ACT
Reinert et al *JAMA Oncol 2019*	I-III	3/10 (30%)
Parikh et al Clin Cancer Res 2021	I-III	1/6 (16.7%)
Tie et al Sci Transl Med 2016	II	3/6 (50%)
Tie et al *JAMA Oncol 2019*	III	5/20 (25%)
Henriksen et al *Clin Cancer Res 2022*	III	4/20 (20%)
Kotaka et al J Clin Oncol, 2022	I-IV	65/96 (67.6%)

Using ctDNA to guide ACT is contingent on ACT being able to clear residual disease

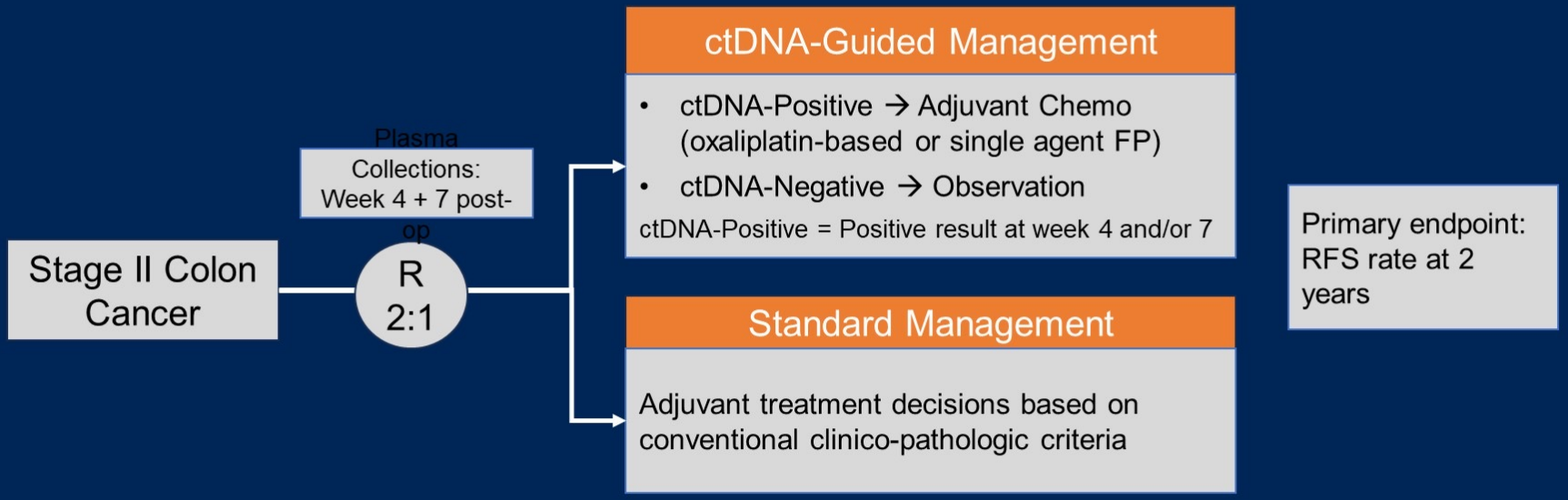
~30% ctDNA+ converted to ctDNA- with ACT

Overview of selected ongoing clinical trials involving ctDNA

- DYNAMIC trial
- BESPOKE CRC study
- GALAXY study
- PEGASUS trial

DYNAMIC Trial

- Prospective, randomized trial in Stage II colon cancer
- Tumor informed assay



Tie et al NEJM 2022

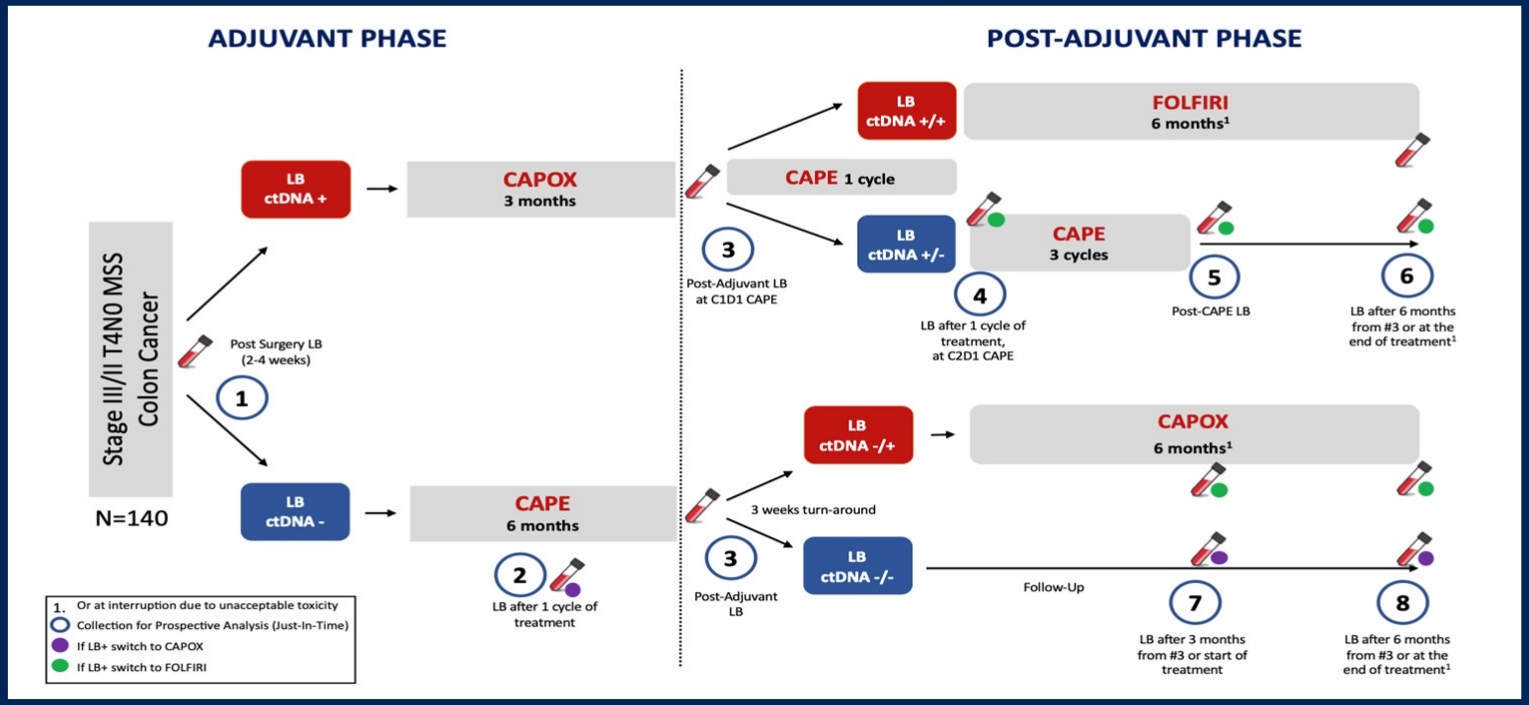
Takeaway points

- Overall, Stage II ctDNA- patients do well, but long-term results needed to adopt de-escalation into practice.

- 6% (15/246) ctDNA- patients had recurrence, highlighting negative ctDNA may miss some cases with residual disease, but combined with traditional risk factors can help risk stratify better and spare toxicity.

PEGASUS Trial

- Prospective feasibility study in high-risk stage II(T4) and stage III CC
- Tumor agnostic assay; Interim 21.2-month analysis



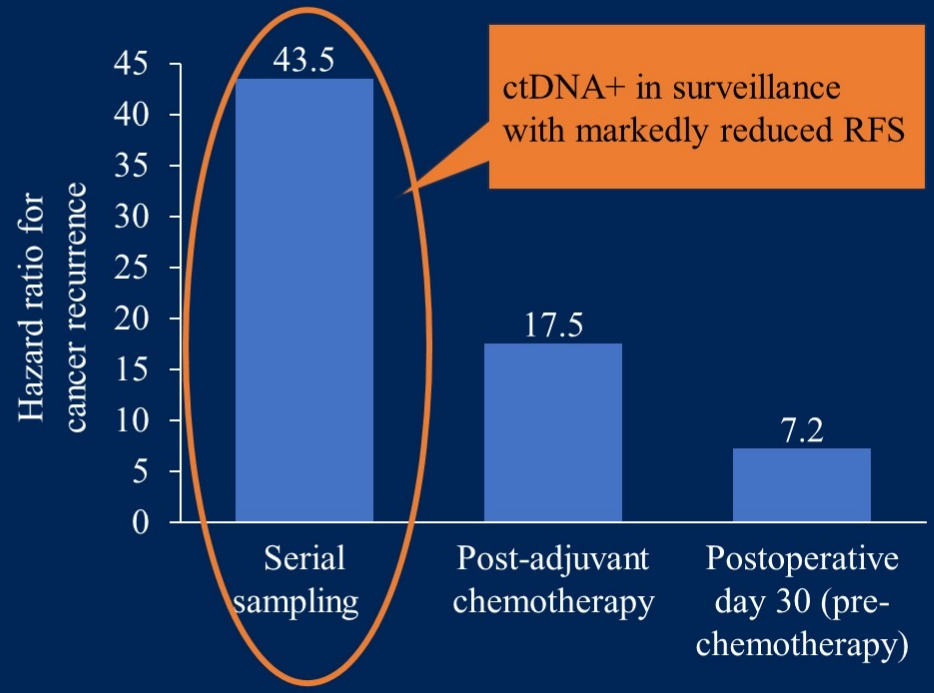
Lonardi ESMO 2023

Primary end-point: false negative rate (10%, 10/100)

- Longer follow up needed for conclusion
- 26% MRD+ post surgery: strongly prognostic (HR 4.37, P=0.0003)
- 40% of MRD + pts seroconverted MRD- at the end of any treatment (CAPOX or escalation to FOLFIRI)
- Lower accuracy of ctDNA to detect local, lung and peritoneal relapses

Lonardi ESMO 2023

ctDNA in surveillance

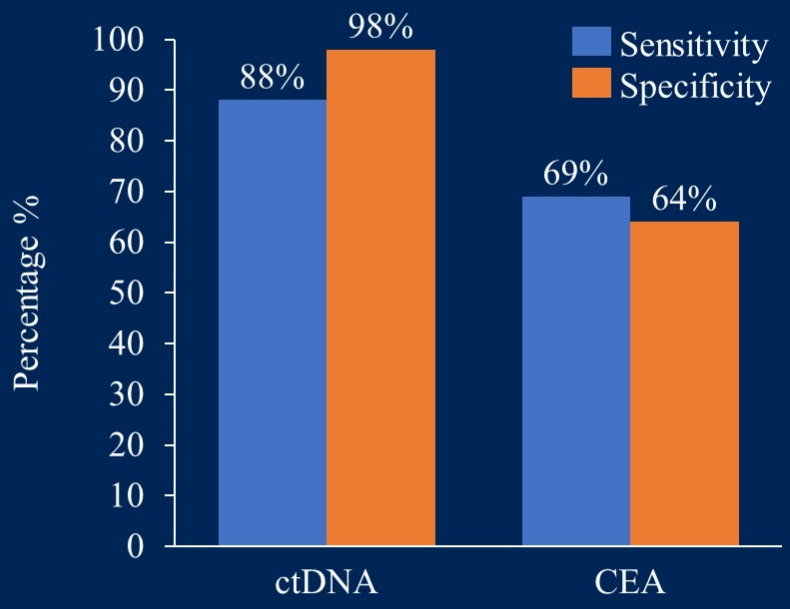


Current std of care: H&P, CEA, imaging, colonoscopy

ctDNA detection can anticipate radiologic recurrence with a lead time of 3 – 12 months

Data adopted from Reinert et al, JAMA Oncol 2019

ctDNA in surveillance



Improved sensitivity and specificity to identify recurrence with serial ctDNA sampling in surveillance

Key question: Can early intervention improve long term clinical outcomes?

Data adopted from Reinert et al, JAMA Oncol 2019

Ongoing Prospective Studies on ctDNA-Guided Management of CRC

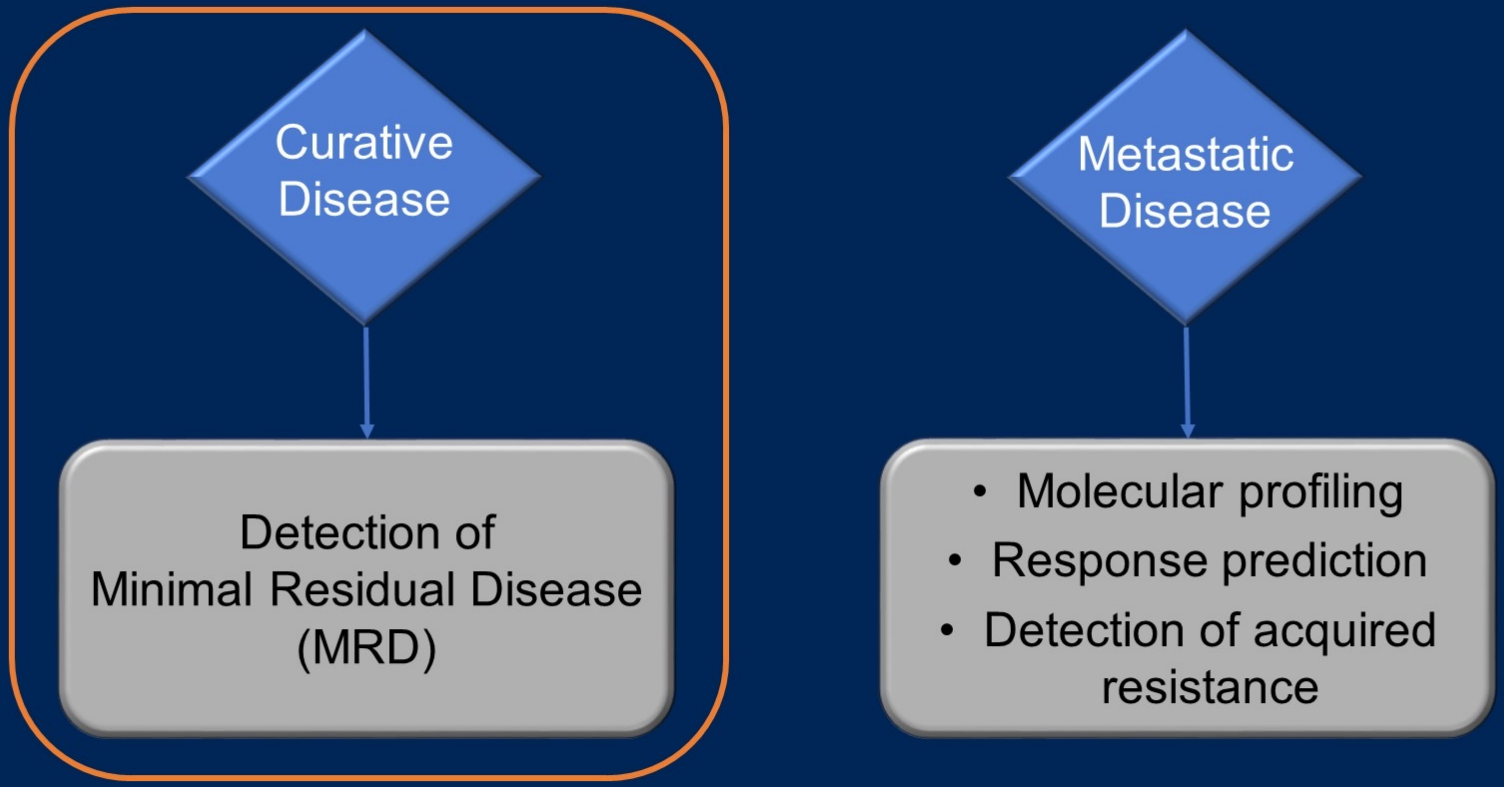
Summary of ctDNA in curative disease

- Unequivocal prognostic risk factor for recurrence; More prognostic than T stage and N status
- ~100% ctDNA+ will recur without intervention
- Current assays capture 40-50% of recurrences. Recurrence risk low if ctDNA- , but not as low as in Stage I disease (~ 3-5%)
- ACT in ctDNA+ cases improves short term outcomes (3y DFS); unclear improves long term cure rates

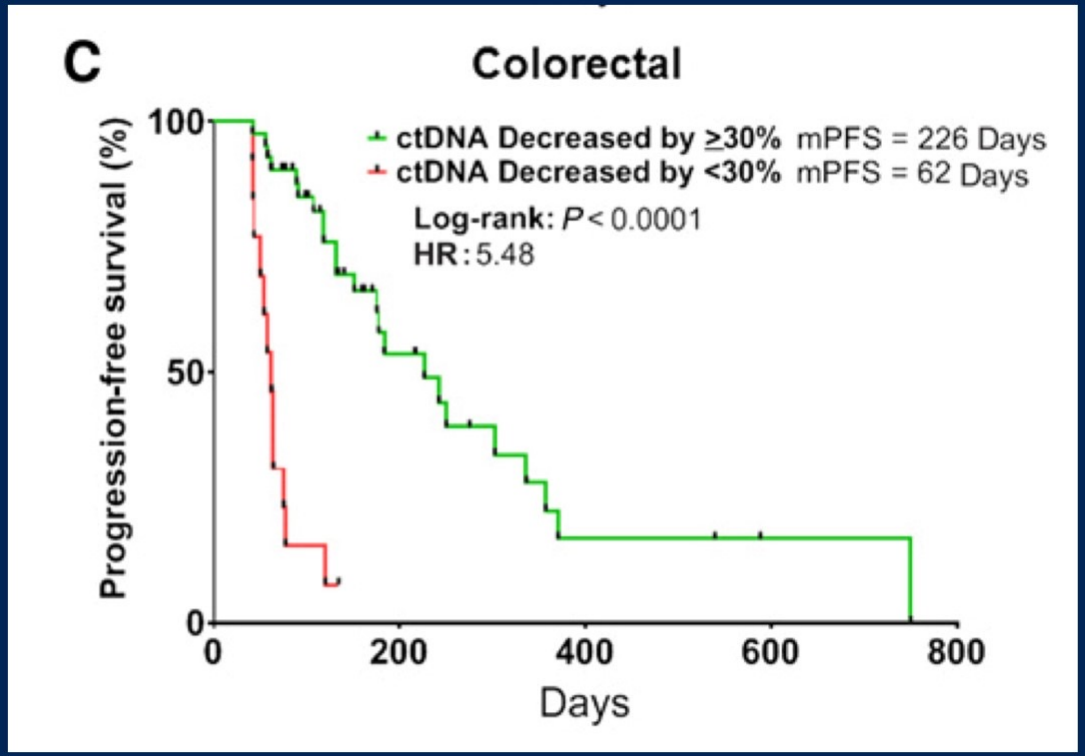
Need higher sensitivity of ctDNA assays for de-escalation!

Escalation in ctDNA+ if adjuvant not planned is reasonable!

ctDNA applications



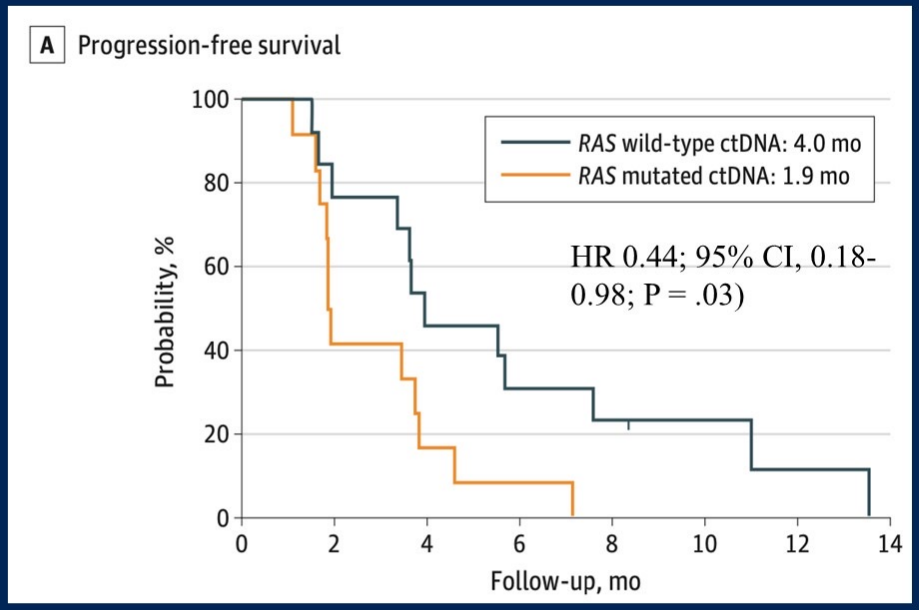
ctDNA is predictive of response & improved clinical outcomes



>= 30% decrease in ctDNA at 4 weeks after treatment initiation with significantly improved PFS

Parikh et al, Clin Cancer Res 2020

ctDNA can detect acquired resistance



CRICKET trial: RAS WT ctDNA with longer PFS on rechallenge with cetuximab + irinotecan in the 3rd line

- **Tumor Heterogeneity:**

ctDNA can identify multiple clinically relevant resistance mechanisms, potentially missed by single lesion biopsy

- **Clonal Decay:**

RAS/RAF/EGFR mutant alleles appear during EGFR blockade can decline upon therapy withdrawal & can be captured by ctDNA

Parikh et al, Nature medicine 2019
Cremolini et al, JAMA Oncol. 2019

Key takeaways

ctDNA is highly prognostic

MRD predicts for clinical recurrence

Current ctDNA assays have low sensitivity to detect MRD

De-escalation of ACT based on negative ctDNA is NOT recommended

ctDNA guided intervention is potentially predictive for improving short term outcomes

Unclear benefit on long term survival

Guidelines do not yet recommend routine ctDNA testing to guide management

Encourage clinical trial enrollment & shared decision making

Summary

Summary & future directions

- Powerful prognostic and potentially predictive biomarker in curative setting.
- Need to increase sensitivity & specificity of assays; Decrease turnaround time & costs.
- MRD applications have tremendous opportunity to guide treatment decisions; awaiting ongoing prospective trial results if early intervention based on ctDNA can improve long term survival.

Practical considerations

- Shared decision making very important!
- Insufficient evidence to recommend use of ctDNA assays outside of a clinical trial given unknown impact on long term survival outcomes.