Transforming Oncology Care
Through Medically Integrated Collaboration

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Clinical Utility of ctDNA in Colon Cancer: Enhancing Precision Oncology

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OBJECTIVES

1. Review current colon cancer treatments and disease monitoring strategies. (P/T/N)

2. Discuss current literature regarding the utility of ctDNA in colon cancer monitoring and current guideline recommendations. (P/T/N)

3. Identify current challenges with implementing ctDNA monitoring in clinical practice. (P/T/N)

4. Describe the utilization of ctDNA for patients with colon cancer based on patient-specific factors. (P/T/N)

DISCLOSURES

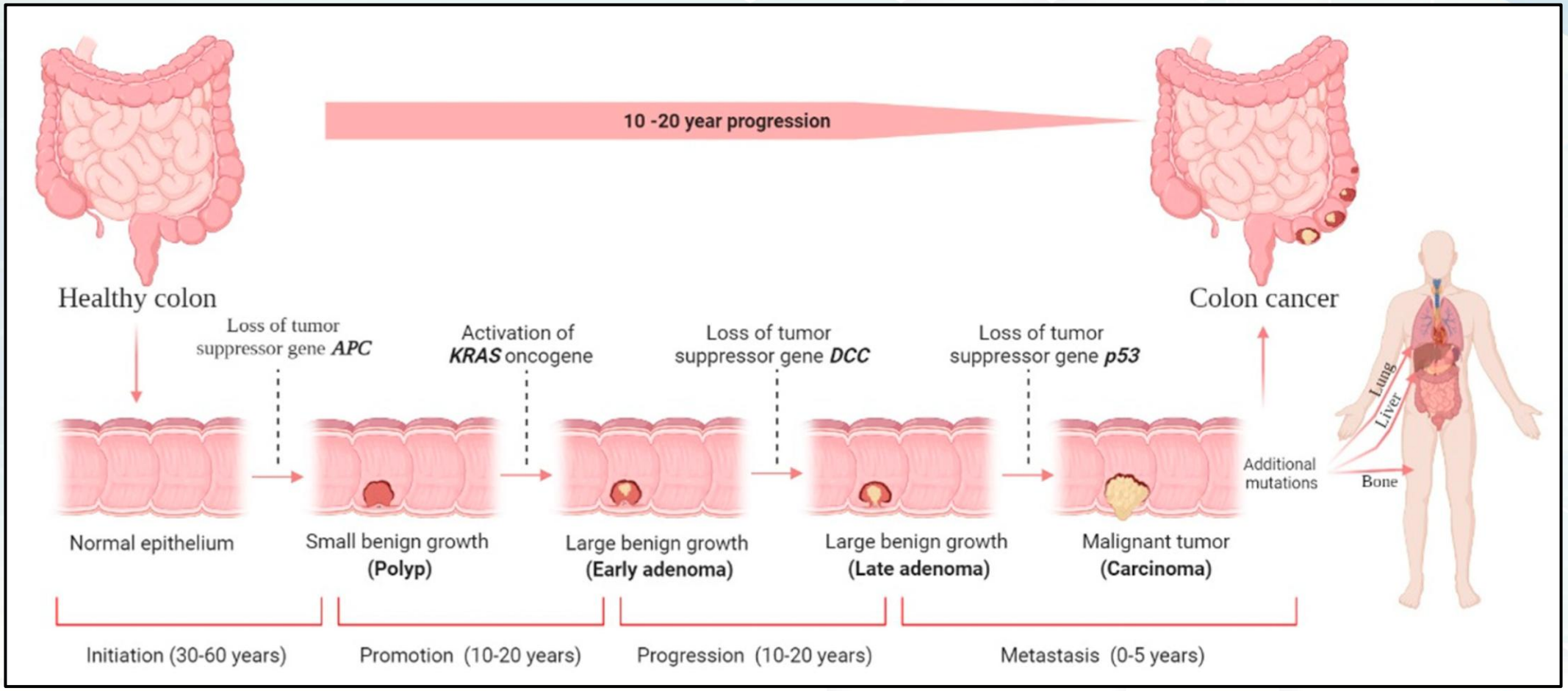
The following relevant financial relationships from the past 24 months have been identified and disclosed for the following faculty of this CE activity:

- Sasha Watson, PharmD
  - Speaker's bureau for Aadi Bioscience, Inc. and Astellas Pharma, Inc.

No relevant financial relationships have been identified for the following planners of this CE activity:

- Stephanie Parker, PharmD
- Tahsin Imam, PharmD
- Daisy Doan, PharmD

Colon Cancer Overview



Hossain MS et al. Cancers (Basel). 2022;14(7):1732.

Colon Cancer Statistics

- **4th** most common cancer type
- **7.6%** of all new cancer cases in the United States
- **152,810** estimated new cases in 2024
- **53,010** estimated deaths in 2024
- **65%** 5-year relative survival
  - **91%** if localized
  - **74%** if regional
  - **16%** if distant
- Concerning rising incidence in younger patients

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Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov)

Adobe stock image/logo

Colon Cancer Presentation

Presentation:

- Changes in bowel movements (diarrhea or constipation)
- Blood in stool
- Weight loss
- Abdominal discomfort
- Nausea/vomiting
- Anemia

Risk factors:

- Obesity
- Red and processed meats
- Smoking
- Alcohol use
- Genetic predisposition (e.g., Lynch syndrome, familial adenomatous polyposis, family history)
- Ulcerative colitis or Crohn’s disease

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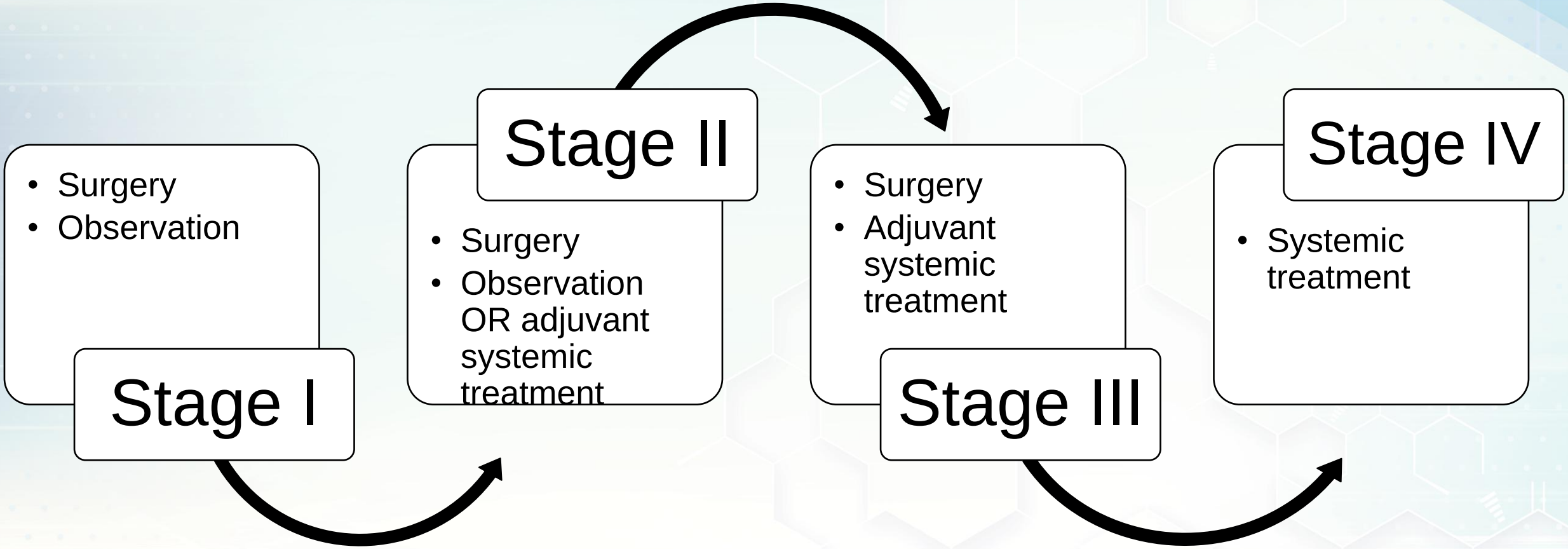
Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov)

Colon Cancer Treatment



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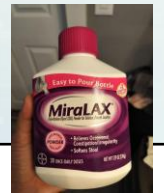
Current Systemic Treatments

Chemotherapy	FOLFOX, FOLFIRI, FOLFOXIRI/FOLFIRINOX, XELOX/CAPEOX, capecitabine, trifluridine-tipiracil (TAS-102)
Anti-VEGF	Bevacizumab, ziv-aflibercept, regorafenib, fruquintinib
Anti-EGFR	Cetuximab, panitumumab
Immune checkpoint inhibitors	Nivolumab, ipilimumab, dostarlimab
Anti-BRAF	Encorafenib
Anti-KRAS G12C	Adagrasib, sotorasib
Anti-HER2	Trastuzumab, pertuzumab, tucatinib, lapatinib, trastuzumab deruxtecan
Anti-NTRK	Larotrectinib, entrectinib, repotrectinib
Anti-RET	Selpercatinib

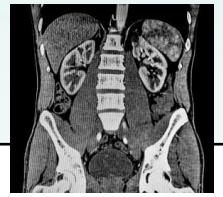
FOLFOX: 5-fluouruacil, oxaliplatin; FOLFIRI: 5-fluouruacil, irinotecan; FOLFOXIRI/FOLFIRINOX: 5-fluouruacil, irinotecan, oxaliplatin; XELOX/CAPEOX: capecitabine, oxaliplatin

How do we monitor colon cancer?



Colonoscopy

- Typically every 5-10 years for screening
- Can detect pre-cancer (polyps)
- Stool test offers less-invasive option, but less accurate



Imaging

- Typically every 2-3 months during treatment
- Typically every 3-6 months during surveillance
- Can miss early cancer development

CEA

- Typically every 2-4 weeks during treatment
- Typically every 3-6 months during surveillance
- May not be accurate depiction of disease control

Clinical Symptoms

- Symptoms may be vague
- Presents after disease progression

ctDNA

- ?

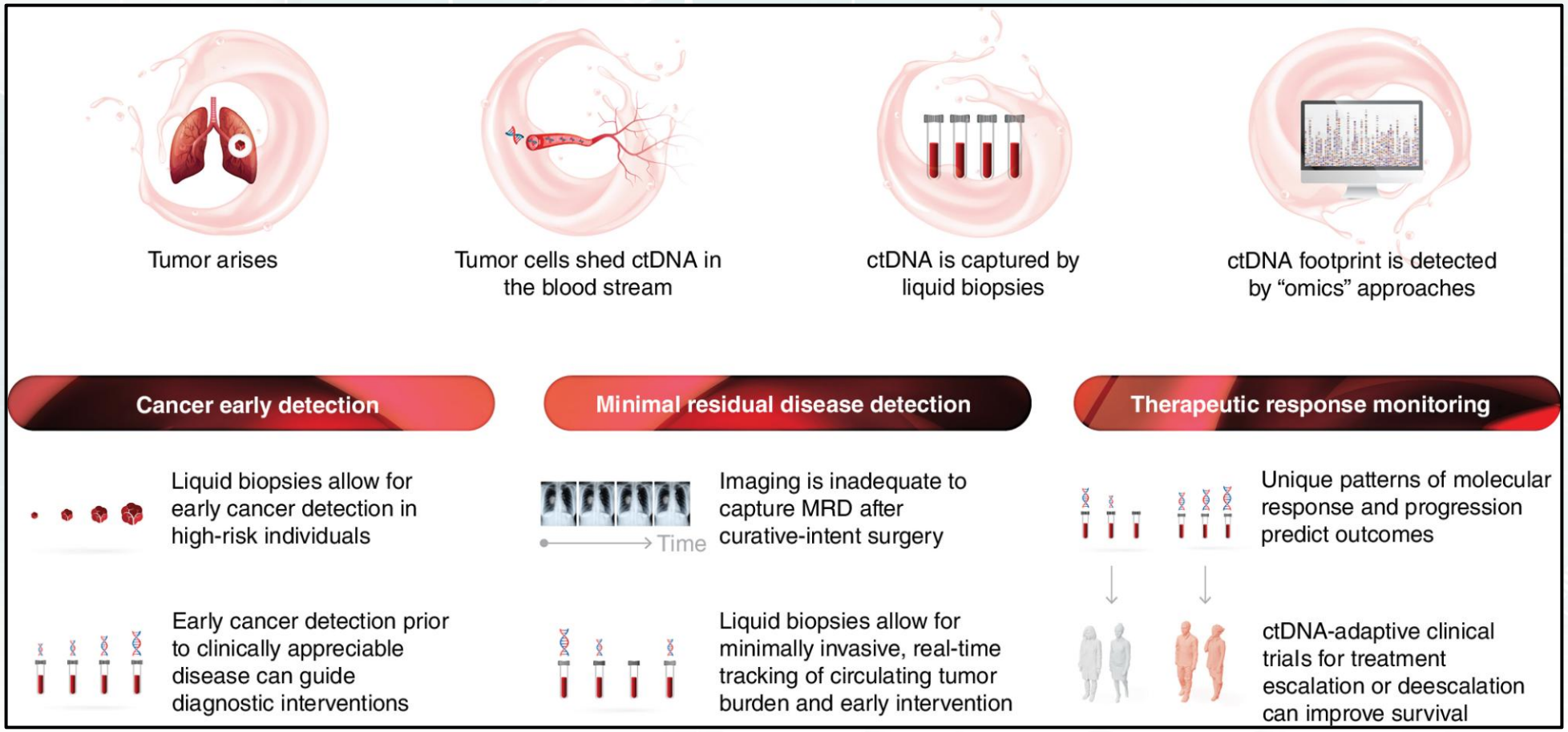
https://www.miralax.com/products/miralax
https://www.nibib.nih.gov/media/34351
Report courtesy of Sylvester Comprehensive Cancer Center at University of Miami
https://www.americanstandard-us.com/

What is ctDNA?

- ctDNA: circulating tumor DNA
- “Liquid biopsy” typically measured from a blood sample (non-invasive)
- May be used in early cancer detection (screening), monitoring of minimal residual disease (MRD), tracking treatment response, and evaluating the tumor’s genomic profile
- Current ctDNA detection rates:
  - 50% in patients with non-metastatic disease
  - 90% in patients with metastatic disease
- Many commercial tests available (e.g., Signatera, Guardant, Northstar)

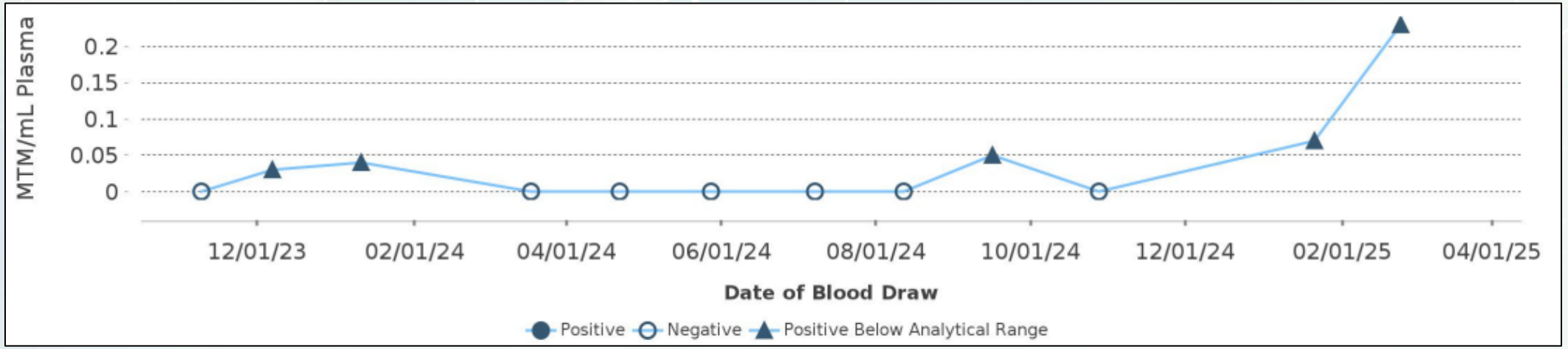
Dasari A et al. Nat Rev Clin Oncol. 2020;17(12):757-770.

What is ctDNA (cont.)?



Anagnostou V et al. Cancer Discov. 2024;14(4):615-619.

ctDNA Report Examples



✓ Approved in indication ~ Approved in other indication ⊗ Lack of response

DETECTED ALTERATION(S) / BIOMARKER(S)	ASSOCIATED FDA-APPROVED THERAPIES	CLINICAL TRIALS (SEE PAGE 5)	% CFDNA OR COPY NUMBER
KRAS G12L	None	Yes	13.5%
TP53 R306*	None	Yes	10.5%

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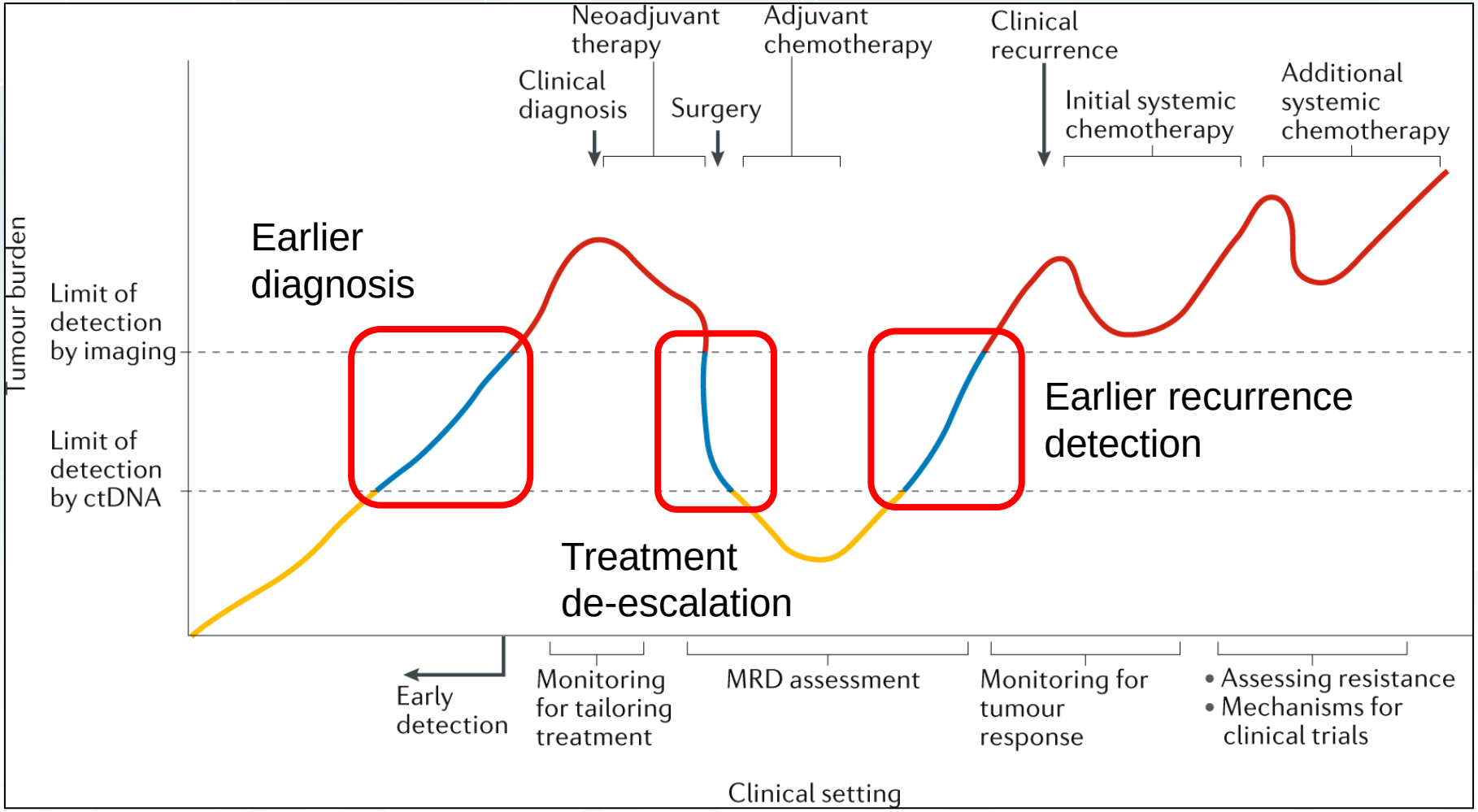
Report courtesy of Sylvester Comprehensive Cancer Center at University of Miami

How can we use ctDNA?



Dasari A et al. Nat Rev Clin Oncol. 2020;17(12):757-770.

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QUESTION 1

Which of the following are options for monitoring colon cancer?

A. Colonoscopy
B. Stool testing
C. Imaging
D. CEA
E. ctDNA
F. All of the above

Current NCCN© Recommendations

- Stage II at high risk for systemic recurrence
  - “Historical high-risk factors for recurrence (exclusive of those cancers that are MSI-H): poorly differentiated/undifferentiated histology; lymphatic/vascular invasion; bowel obstruction; <12 lymph nodes examined; perineural invasion (PNI); localized perforation; close, indeterminate, positive margins; or high-tier tumor budding. In patients with high-risk, stage II disease, there are no data that correlate risk features and selection of chemotherapy.
  - **ctDNA is prognostic, but not predictive.”**

Current NCCN© Recommendations (cont.)

- Adjuvant treatment
  - “Circulating tumor (ctDNA) is a prognostic marker; however, there is **currently insufficient evidence** to recommend routine use of ctDNA assays outside of a clinical trial. De-escalation of care and treatment decision-making are not recommended based on ctDNA results. Participation in clinical trials is encouraged.”

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Current NCCN© Recommendations (cont.)

- Stage II-III surveillance
  - "ctDNA is **not recommended** for surveillance."

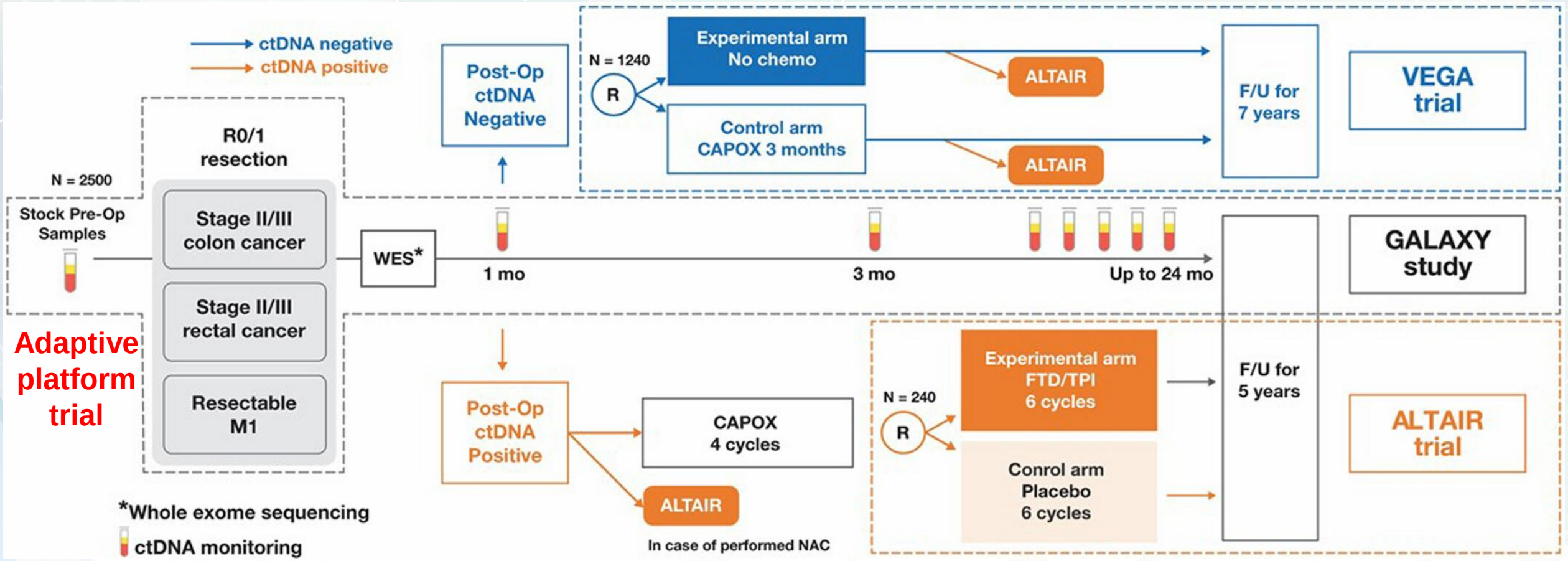
Why is ctDNA not routinely recommended at this time?

Current ctDNA Trials in Colorectal Cancer

- ctDNA for MRD detection: is it an accurate tool to improve clinical outcomes?
  - CIRCULATE-Japan (GALAXY)
  - BESPOKE
- ctDNA to guide need for adjuvant chemotherapy: can we help cure more patients that need treatment and reduce toxicities for those that don't?
  - DYNAMIC
  - COBRA
  - INTERCEPT
- Metastatic: can we stop or change treatment earlier if it's not working?
  - TACT-D
- **Many others ongoing…**

Taniguchi H et al. Cancer Sci. 2021;112(7):2915-2920.
Kasi PM et al. BMJ Open. 2021;11(9):e047831.
Tie J et al. N Engl J Med. 2022;386(24):2261-2272.
Verbus EA et al. Ann Surg Oncol. 2021;28(8):4095-4097.
Dasari A et al. J Clin Oncol. 2023;41(16):s.
Raghav KPS et al. J Clin Oncol. 2024;42(17):s.

CIRCULATE-JAPAN



ctDNA: circulating tumor DNA; F/U: follow up; FTD/TPI: trifluridine/tipiracil; mo: month; NAC: neoadjuvant chemotherapy; Op: operative; WES: whole-exome sequencing

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Taniguchi H et al. Cancer Sci. 2021;112(7):2915-2920.

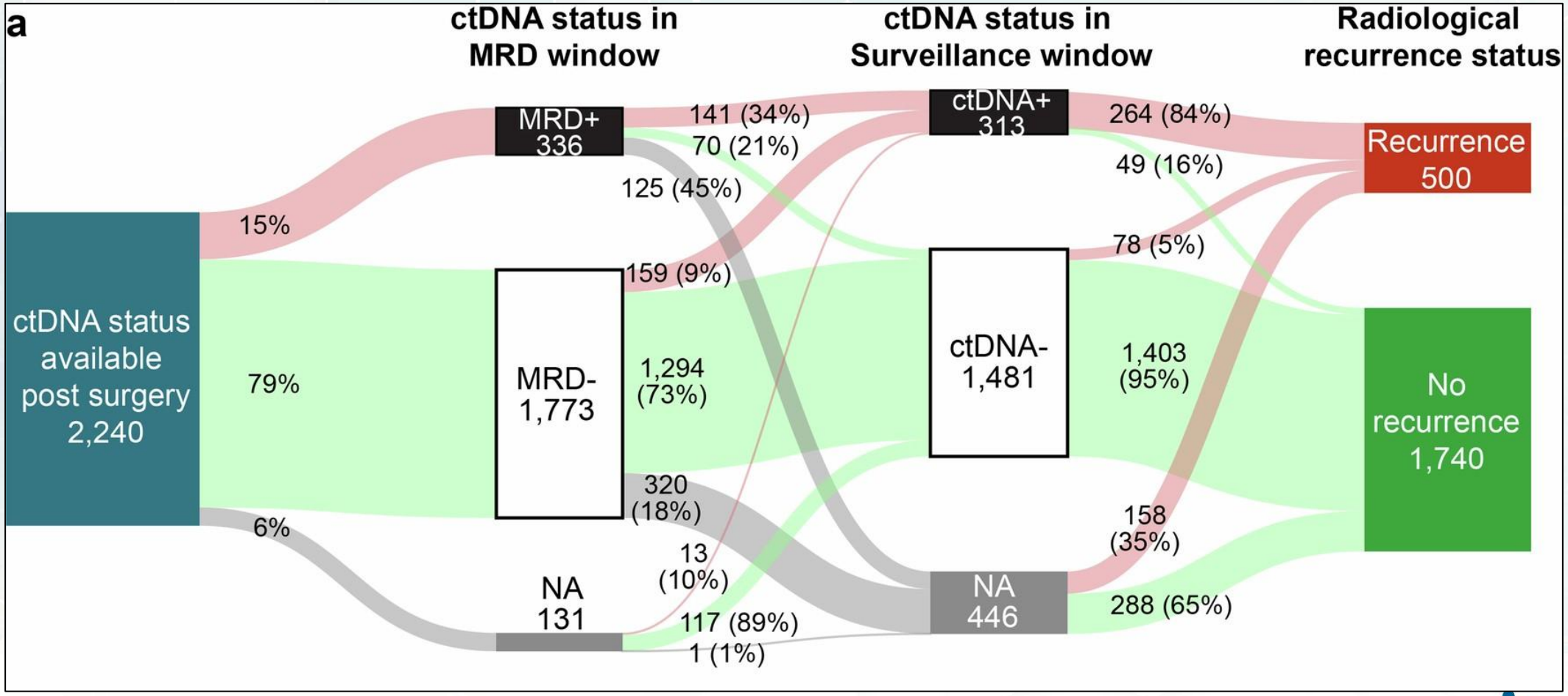
CIRCULATE-JAPAN (cont.)

- GALAXY (interim analysis):
  - N=2518 patients with stage II-IV colorectal cancer after radical resection
  - Improved disease-free survival if MRD(+) vs. MRD(-) by ctDNA (HR 15.75, p<0.0001)
  - Higher recurrence risk if remained ctDNA(+) (HR 5.4, p<0.0001)
  - ctDNA-based MRD detection and response to adjuvant chemotherapy were **highly prognostic** of patient outcomes

- **VEGA and ALTAIR (ongoing)**
  - Will help inform us on role of adjuvant chemotherapy if MRD(-) by ctDNA

Nakamura Y et al. Nat Med. 2024;30(11):3272-3283.

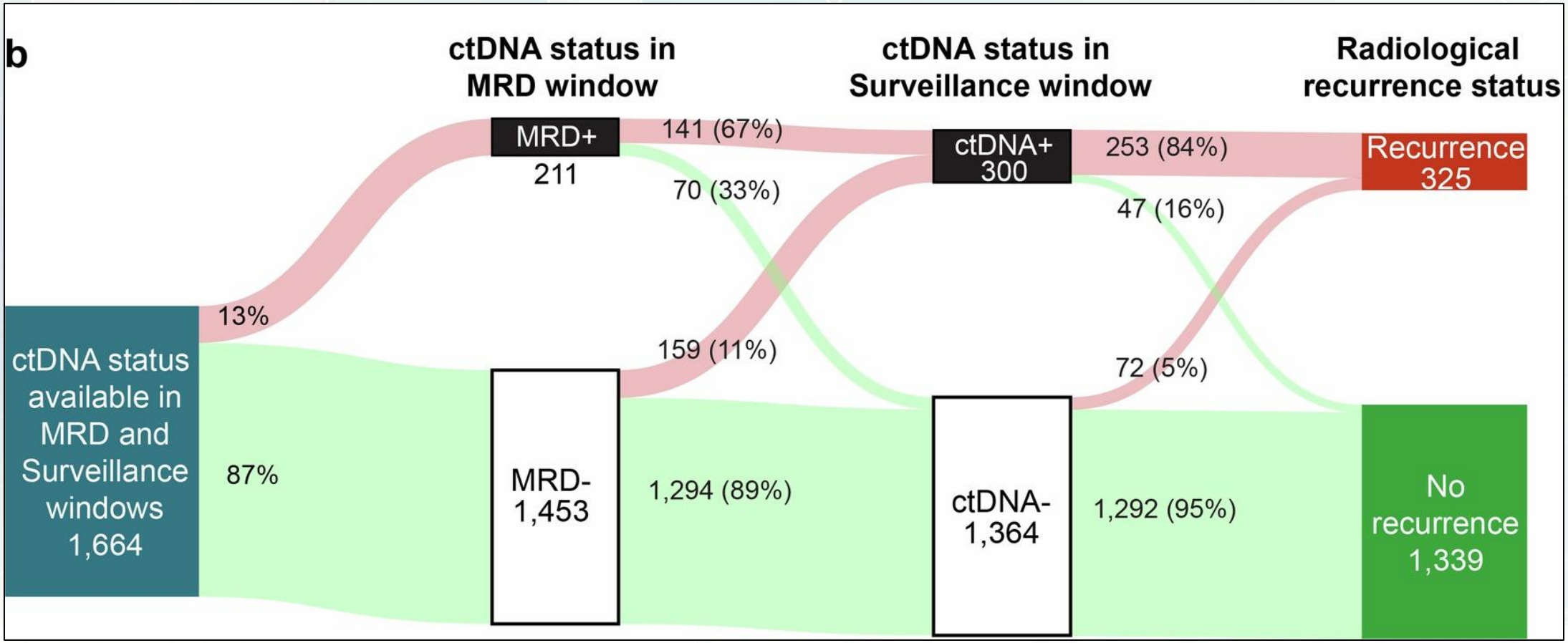
CIRCULATE-JAPAN: GALAXY



MRD: molecular residual disease; NA: not available

Nakamura Y et al. Nat Med. 2024;30(11):3272-3283.

CIRCULATE-JAPAN: GALAXY (cont.)



MRD: molecular residual disease; NA: not available

Nakamura Y et al. Nat Med. 2024;30(11):3272-3283.

BESPOKE (interim analysis)

- N=350 patients with stage II-III colorectal cancer
- 16% of stage II and 22% of stage III patients were ctDNA(+) after resection
- MRD(+) by ctDNA(+):
  - Associated with **inferior disease-free survival** (HR 20.8, p <0.0001)
  - **Longer disease-free survival with adjuvant chemotherapy** vs. observation (12.7 vs. 6.7 months, p=0.01)
  - ctDNA clearance in 39% at 12-weeks post-surgery and associated with **improved disease-free survival** (24.2 vs. 13.8 months, p=0.045), but **worse disease-free survival compared to MRD(-) patients post-surgery**
  - **Recurrence in 44%** (all detected by ctDNA **before radiological detection**)
- MRD (-) by ctDNA(-): **no benefit with adjuvant chemotherapy** (HR 1.1, P=0.89)

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Kasi PM et al. BMJ Open. 2021;11(9):e047831.

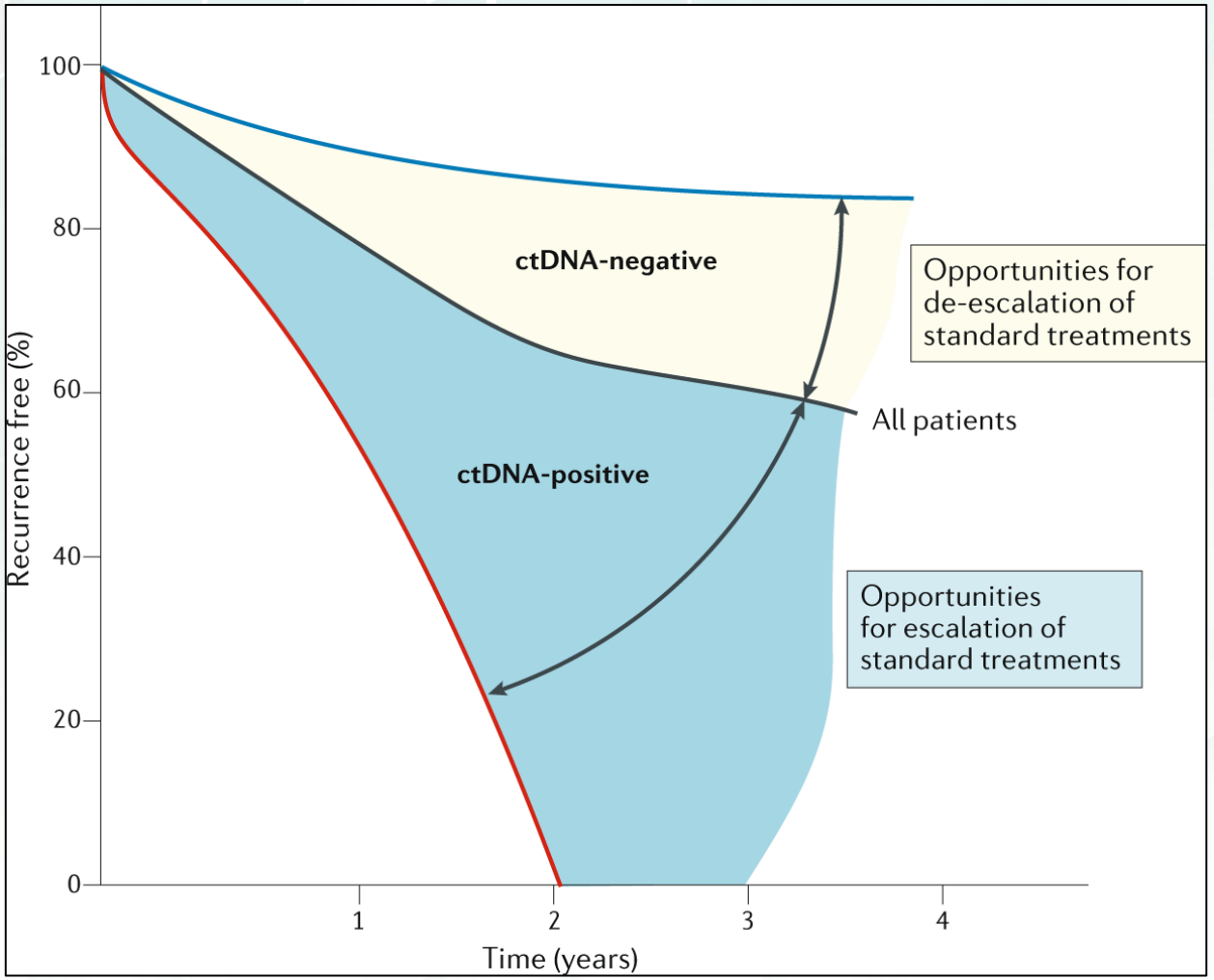
QUESTION 2

True or False: Detection of MRD(+) by ctDNA(+) is associated with worse clinical outcomes based on current literature.

A. True

B. False

How can ctDNA guide treatment?



Dasari A et al. Nat Rev Clin Oncol. 2020;17(12):757-770.

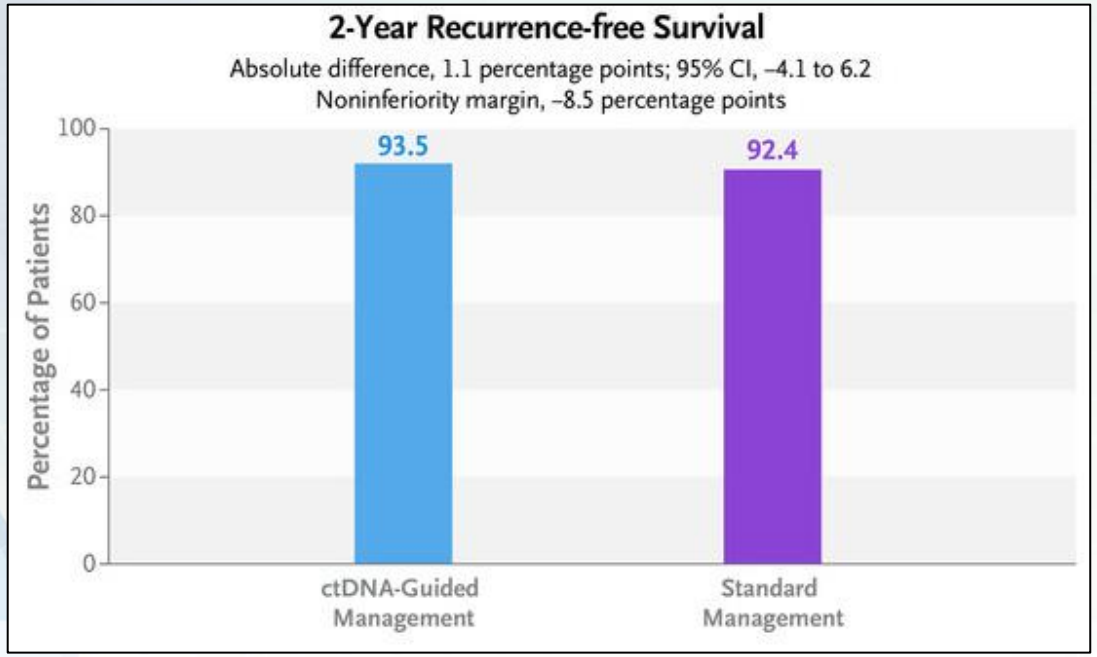
DYNAMIC

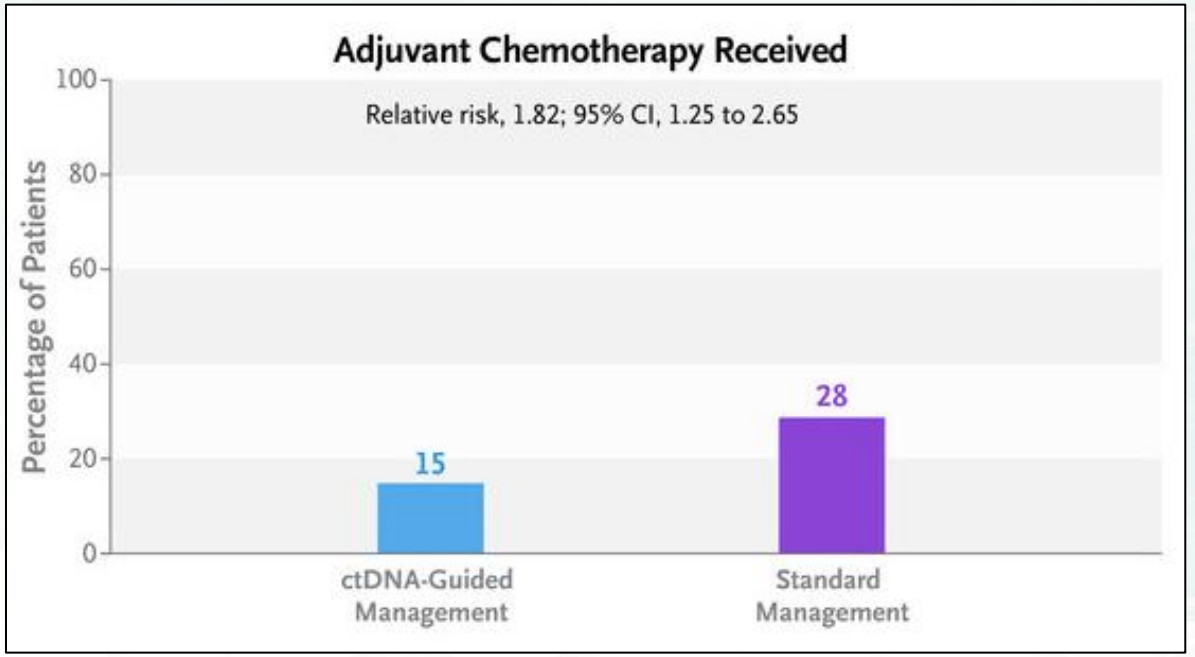
- N=455 patients with stage II colon cancer randomized 2:1 to ctDNA-guided adjuvant chemotherapy vs. standard approach
  - ctDNA-guided (collected at week 4 and 7):
    - Positive ctDNA: adjuvant chemotherapy
    - Negative ctDNA: surveillance
  - Standard approach:
    - Decision for adjuvant chemotherapy based on conventional criteria (e.g., poorly differentiated/undifferentiated, lymphatic/vascular invasion, bowel obstruction)

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

DYNAMIC (cont.)

ctDNA-guided management was **noninferior** to standard management (2 and 5-year follow-up) and resulted in **reduced use of adjuvant chemotherapy**





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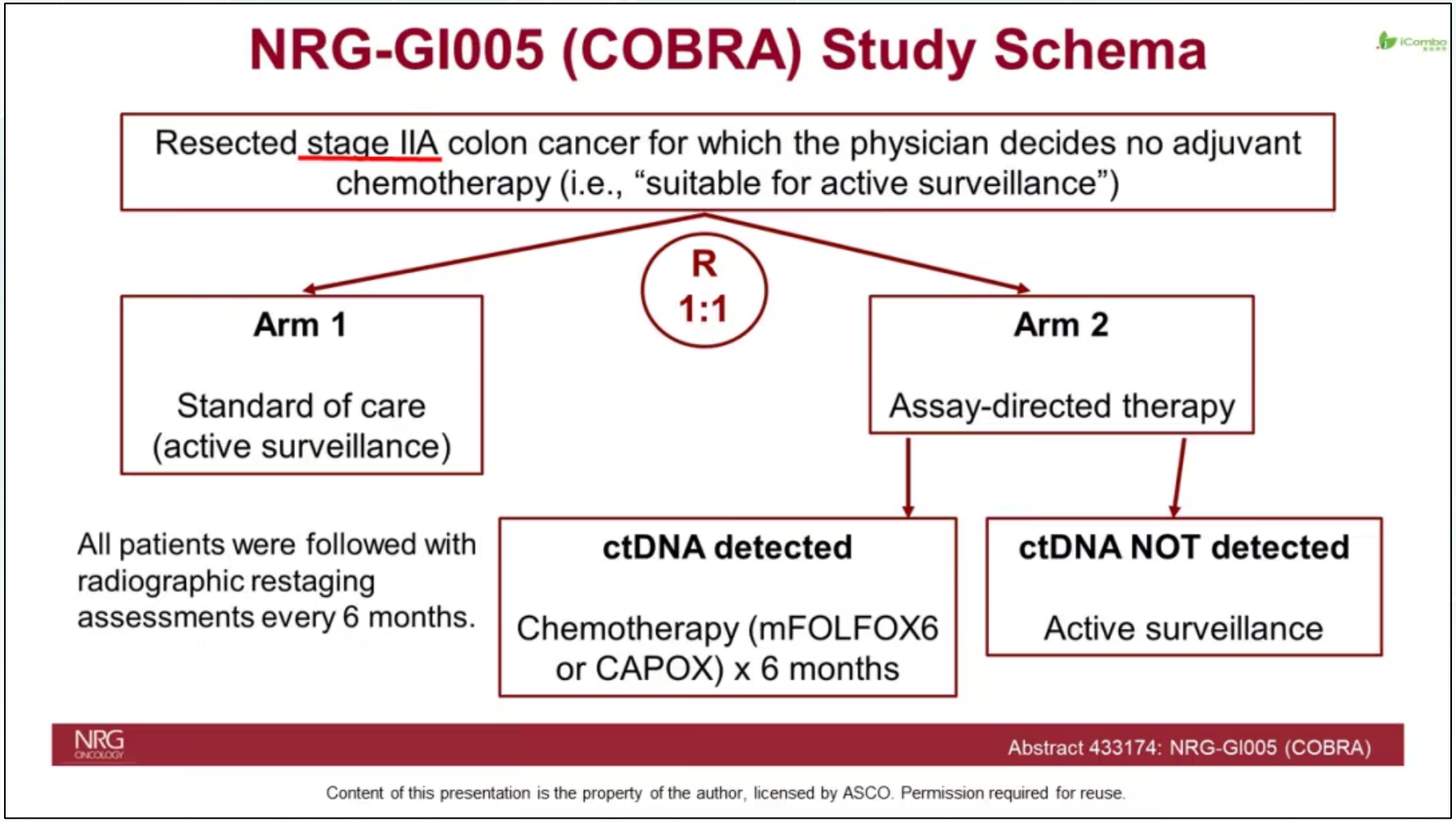
Tie J et al. N Engl J Med. 2022;386(24):2261-2272.

COBRA



Verbus EA et al. Ann Surg Oncol. 2021;28(8):4095-4097.

COBRA (cont.)

- N=1408 patients with resected stage IIa colon cancer
- Trial closed early due to lack of benefit with adjuvant chemotherapy
- Unusually low ctDNA clearance with chemotherapy (11%) vs. high ctDNA clearance rate without chemotherapy (43%)
- Raises concern that ctDNA is **NOT** ready for clinical practice

Verbus EA et al. Ann Surg Oncol. 2021;28(8):4095-4097.

INTERCEPT Program at MD Anderson

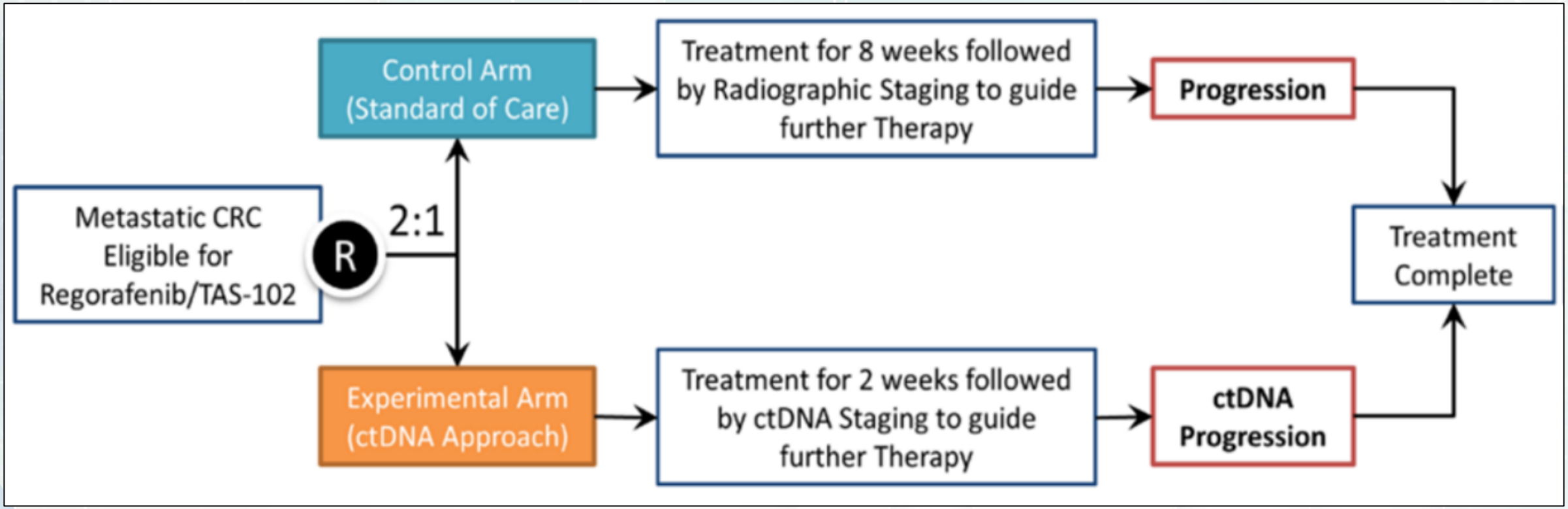
- N=1259 patients with stage I-IV colorectal cancer

- ctDNA(+) in 15% post-surgery
  - Confirmed radiologic progression in 53% of ctDNA(+) patients during surveillance (**reflex imaging**)
  - ctDNA(+) patients without radiologic progression referred for MRD(+) trial of trifluridine/tipiracil (TAS-102)
    - **Improved ctDNA clearance and disease-free survival** in patients receiving TAS-102 vs. historical controls

Dasari A et al. J Clin Oncol. 2023;41(16):s.

Pellatt AJ et al. J Clin Oncol. 2024;42(16):s

TACT-D



CRC: colorectal cancer, ctDNA: circulating tumor DNA

Raghav KPS et al. J Clin Oncol. 2024;42(17):s.

TACT-D (cont.)

- N=80 patients with metastatic colorectal cancer eligible for regorafenib or trifluridine-tipiracil (TAS-102)
- Baseline ctDNA was strongly prognostic for clinical benefit
- Change in ctDNA from C1D1 to C1D15 was predictive of clinical outcomes

Raghav KPS et al. J Clin Oncol. 2024;42(17):s.

Which monitoring tool is best after resection?

True positives =

True negatives =

Table 3. Sensitivity, Specificity, PPV, and NPV for ctDNA, Imaging, and CEA

Measure	Detection method, % (95% CI)			
	ctDNA	Imaging	CEA level	Imaging plus CEA level
Sensitivity	53.3 (27.4-77.7)	60.0 (32.9-82.5)	20.0 (5.3-48.6)	73.3 (44.8-91.1)
Specificity	100 (87.0-100)	96.9 (82.5-99.8)	90.9 (74.5-97.6)	87.9 (70.9-96.0)
PPV	100 (59.8-100)	90.0 (54.1-99.5)	50.0 (13.9-86.1)	73.3 (44.8-91.1)
NPV	82.5 (66.6-92.1)	84.2 (68.1-93.4)	71.4 (55.2-83.8)	87.9 (70.9-96.0)
	Best specificity, but many false positives	Less false positives vs. ctDNA, but may miss some patients with recurrence	Nonspecific with too many false positives	Catches more patients with recurrence vs. CEA alone

CEA: carcinoembryonic antigen, ctDNA: circulating tumor DNA, NPV: negative predictive value, PPV: positive predictive value

Fakih M et al. JAMA Netw Open. 2022;5(3):e221093.

Is ctDNA perfect? No

False positives

- Added stress and anxiety for patients
- Unnecessary treatments
- Additional healthcare system costs

False negatives

- May miss finding true disease recurrence

Current Challenges with ctDNA

- We don’t know enough yet, and it is **NOT** perfect
  - False positives (unnecessary anxiety)
  - False negatives (false hope)
  - Variable clearance rates after adjuvant chemotherapy (17-87%)
  - Reduced utility in lung, peritoneal, and brain metastases
- Studies confirm ctDNA-negativity has good prognostic value, but can we help if ctDNA(+)? Is it too late? **Are we really helping cure more patients?**
- Additional clinic workload coordinating testing
- High cost

Does adjuvant therapy help if ctDNA(+)?

Study	Stage	Ability of Adjuvant Therapy to Convert ctDNA-Positive to ctDNA-Negative (% of ctDNA clearance postoperatively)
Reinert et al[25]	I-III	3/10 (30)
Parikh et al[15]	I-III	1/6 (16.7)
Tie et al[16]	II	3/6 (50)
Tie et al[17]	III	5/20 (25)
Henriksen et al[18]	III	4/20 (20)
Tie et al[20]	IV	3/11 (27.3)
Kotaka et al[24]	I-IV	65/96 (67.7)

ctDNA: circulating tumor DNA

Maybe, but it's not curing everyone

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Malla M et al. J Clin Oncol. 2022;40(24):2846-2857.

Who should receive ctDNA monitoring?

- Discussion between oncologist in patient
  - ctDNA is not perfect, but may help us learn more about your cancer and detect cancer before we can see it on scans
  - ctDNA monitoring may add more anxiety if positive
  - ctDNA monitoring will require more lab draws and you may incur additional costs
  - **Do the positives outweigh the negatives?**

- Most data supports use in the curative setting after surgical resection

QUESTION 3

True or False: Current literature confirms that all ctDNA(-) patients should not receive adjuvant chemotherapy after surgery since it can do more harm than good.

A. True

B. False

QUESTION 4

Your patient was just diagnosed with colon cancer and wants to know if they should receive testing for ctDNA. Which of the following best describes the current utility of ctDNA for colon cancer?

A. All patients should receive ctDNA testing
B. ctDNA testing yields 100% sensitivity and specificity
C. A negative ctDNA result after surgery guarantees a cure
D. ctDNA offers a less invasive monitoring tool which may help guide treatment decisions when used in conjunction with imaging, CEA, and other clinical features

SUMMARY

- MRD detection by ctDNA is a prognostic tool in colon cancer
- ctDNA monitoring after resection may help to avoid unnecessary adjuvant therapy (less toxicity)
- ctDNA can capture treatment resistance with molecular profiling
- ctDNA appears to be a promising tool to help guide treatment decisions in **combination** with imaging, CEA, and other clinical features, but we still need to learn more before implementing into clinical practice as the new “gold standard”
- The future is bright and we are getting closer to curing cancer with exciting advancements including ctDNA

QUESTION & ANSWER

Clinical Utility of ctDNA in Colon Cancer: Enhancing Precision Oncology

Sasha Watson, PharmD

Outpatient Medical Oncology Clinical Pharmacist (GI + Sarcoma)

Sylvester Comprehensive Cancer Center at University of Miami

CE CODES

Clinical Utility of ctDNA in Colon Cancer: Enhancing Precision Oncology