



Annual

**Advances and Innovations in Endoscopic Oncology  
and Multidisciplinary Gastrointestinal Cancer Care**

# **Early Detection and Precision Interception: Guiding Colorectal Cancer Management with Circulating Tumor DNA (ctDNA)**

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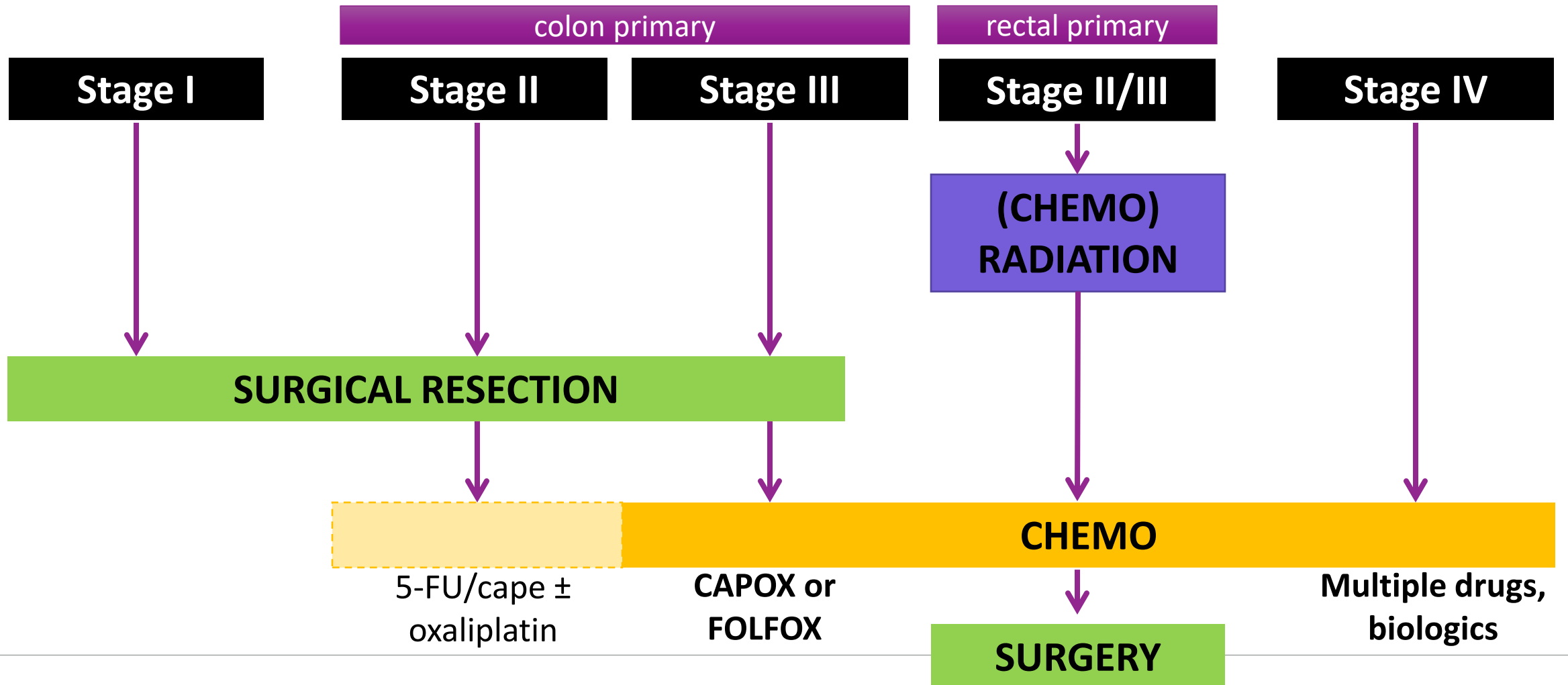
Professor, Clinical Research Division, Fred Hutch Cancer Center



# Disclosures

- This is a Non-CME Accredited session.

# CRC treatment overview



# Case scenario: stage II colon cancer

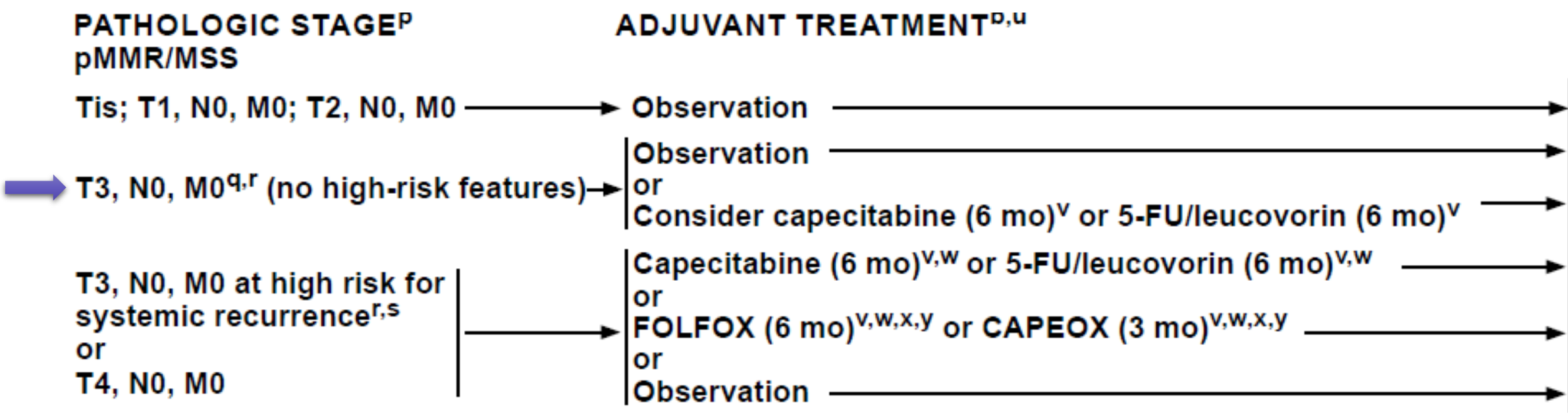
41yo woman presents with rectal bleeding

- Colonoscopy: ulcerated, fungating mass in the sigmoid colon.
  - Biopsy: invasive, moderately differentiated adenocarcinoma
- CT CAP: no evidence of metastatic disease
- Oncologic resection: T3N0. 4.2cm moderately differentiated adenocarcinoma
  - No evidence of lymphovascular or perineural invasion. Low tumor budding. Negative margins.
  - 0/16 lymph nodes with cancer, no tumor deposits.
  - Microsatellite stable (MSS) by next generation sequencing



# Stage 2: current standard-of-care

- Treated with a partial colectomy followed by consideration of adjuvant therapy
  - Effectively guessing who needs additional therapy



# Need for better biomarkers

- Pathologic features guide treatment, but do not reliably predict who will recur



**OncotypeDx:** 14-gene panel of great interest

- Prognostic, but not predictive of chemotherapy benefit



**Microsatellite instability** (~15% stage II)

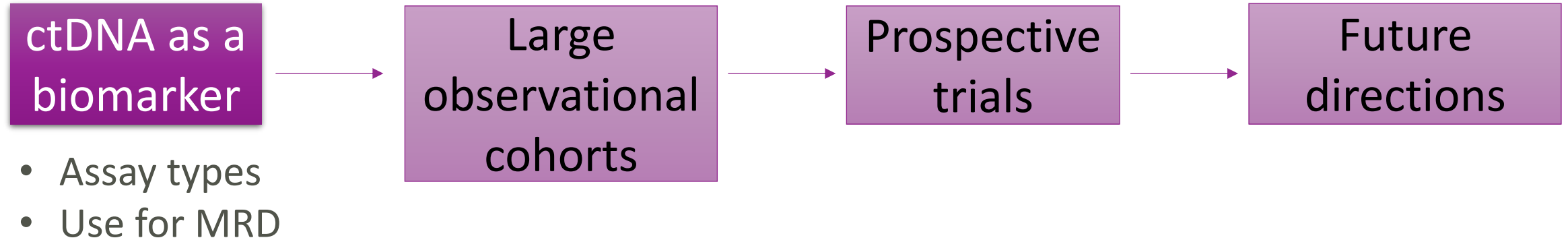
- Good prognosis
- MSI patients do NOT benefit from adjuvant chemotherapy



**ctDNA**

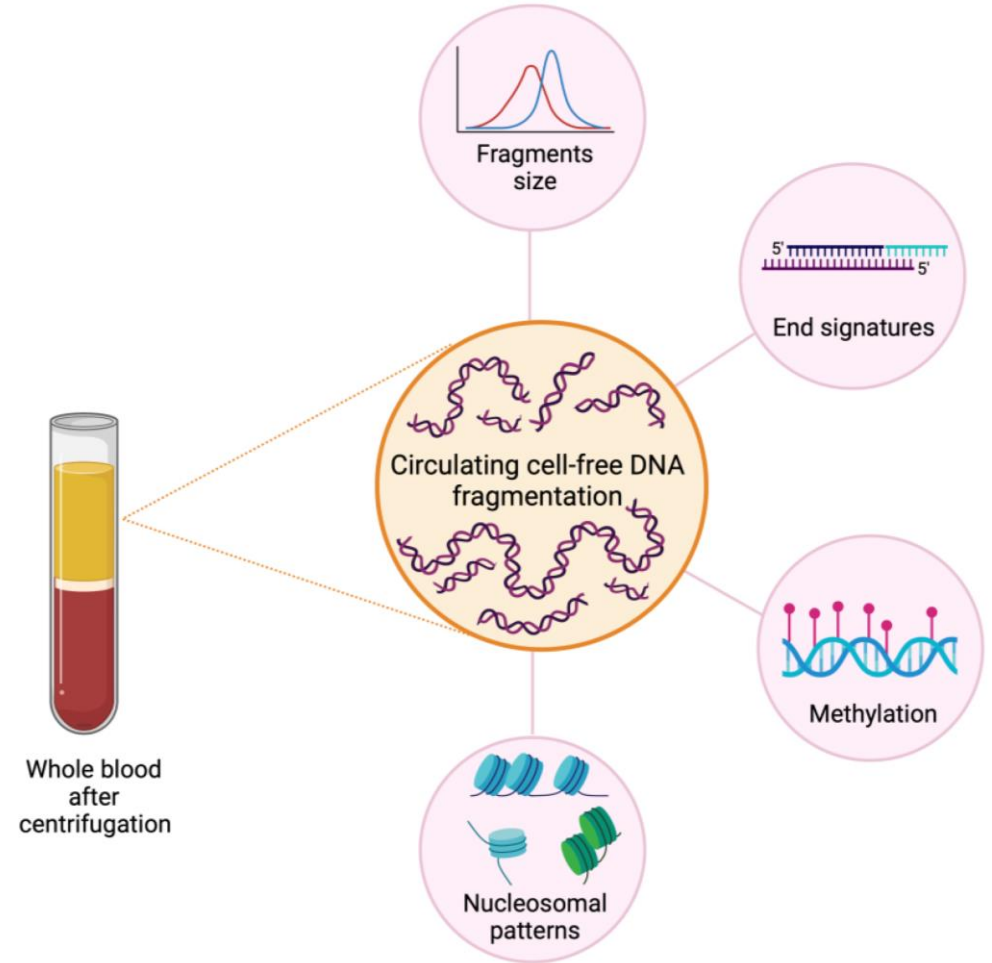
- Associated with a poor prognosis
- Role in predicting chemotherapy response???

# State of the data on ctDNA in colorectal cancer

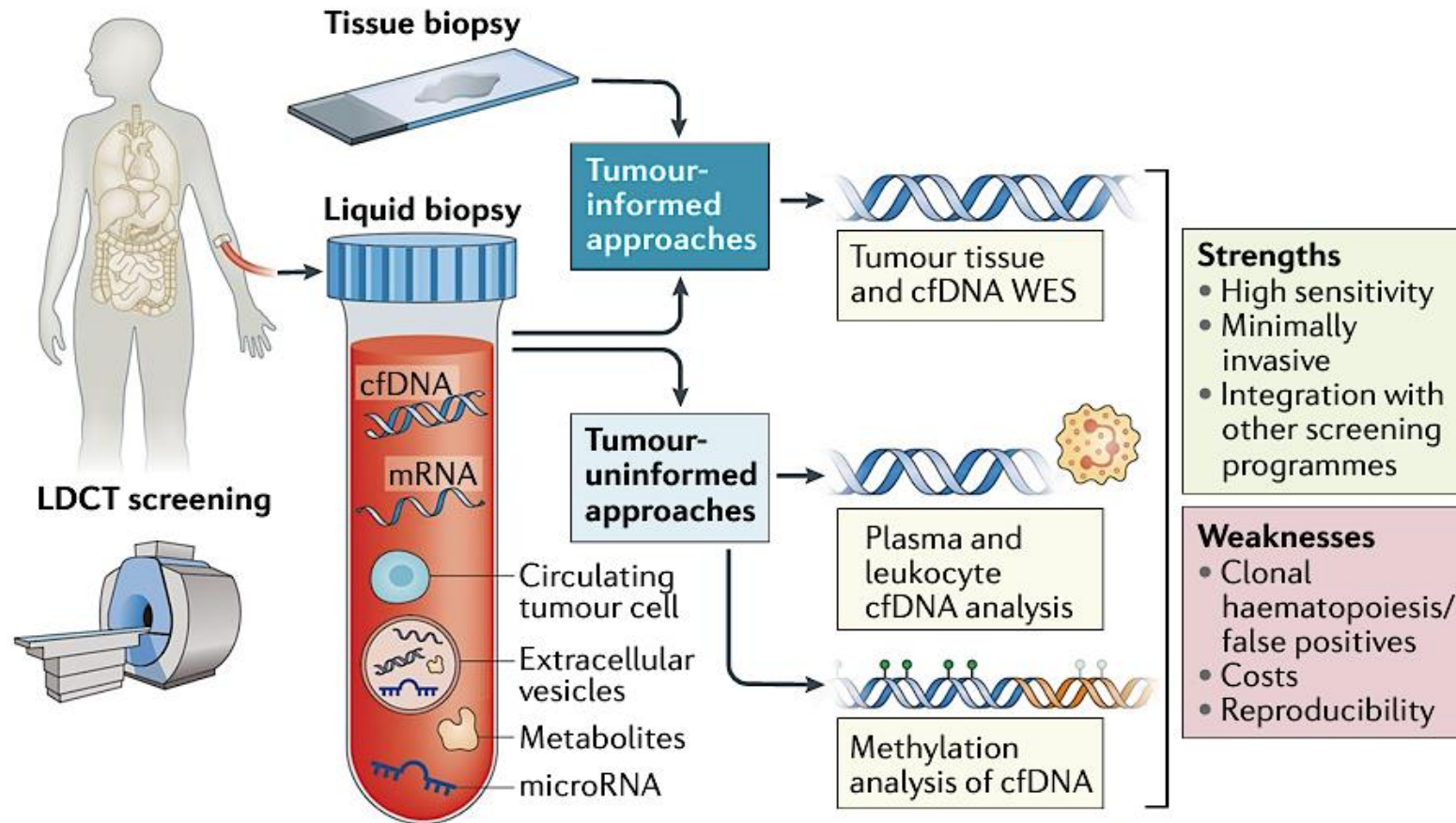


# Defining circulating tumor DNA (ctDNA)

- Low levels of cell-free DNA (cfDNA) can be detected even in the plasma of healthy individuals (1-10 ng/ml)
- ctDNA = detecting mutations in cfDNA that are highly specific for cancer
  - Differences in genetic, epigenetic alterations
  - Different fragment sizes
- Half-life: <2 hours
  - May fluctuate after trauma (surgery), chemotherapy

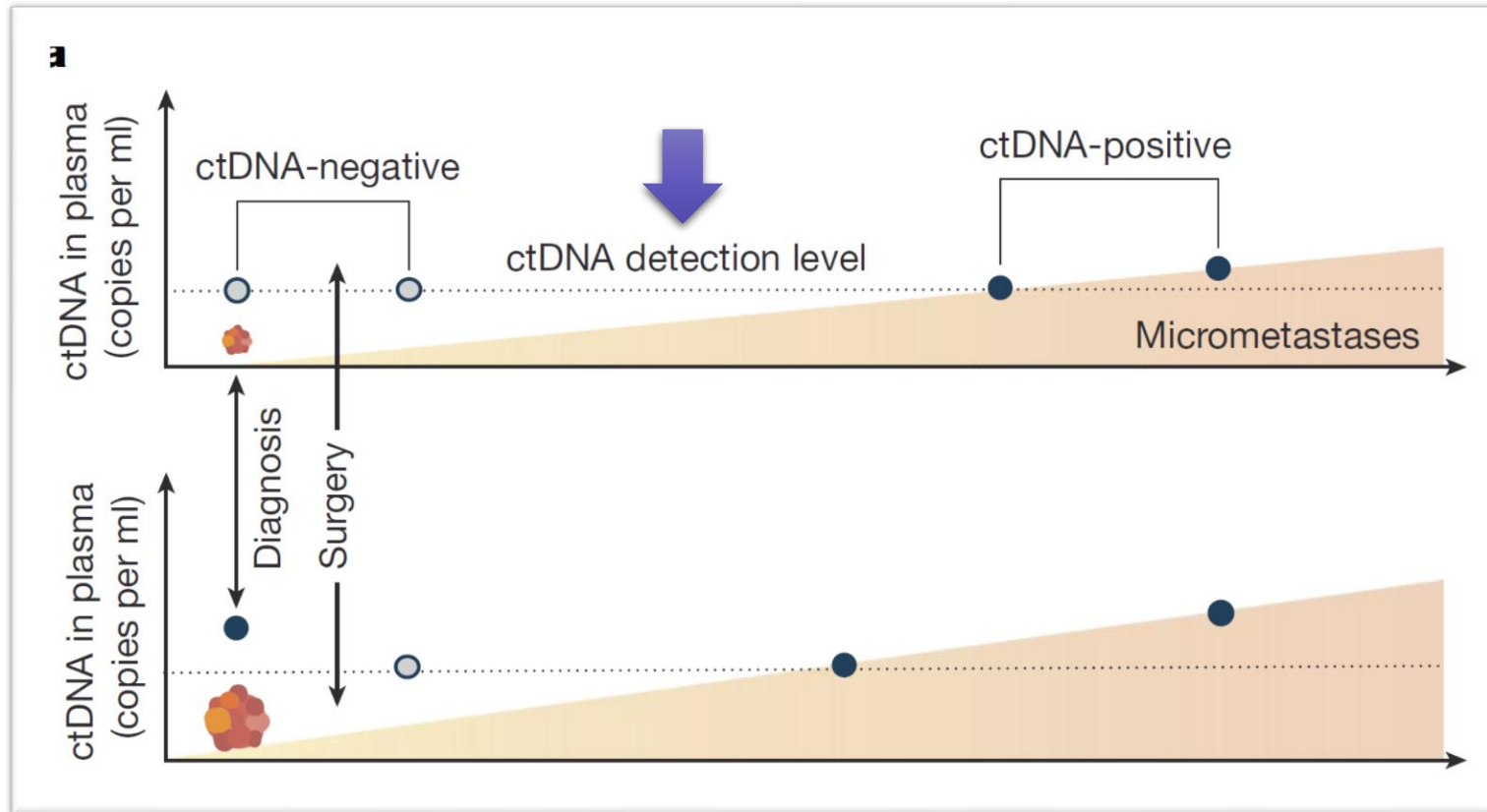


# Tumor-informed vs tumor agnostic



- Tumor-informed vs. tumor-uninformed (a.k.a. tumor-naïve, plasma only)
  - Blood results typically return in 7-14 days
- Tumor-informed approaches may be more sensitive for MRD
  - Longer turnaround time for initial test result (~4-6 weeks)

# Role of longitudinal collection



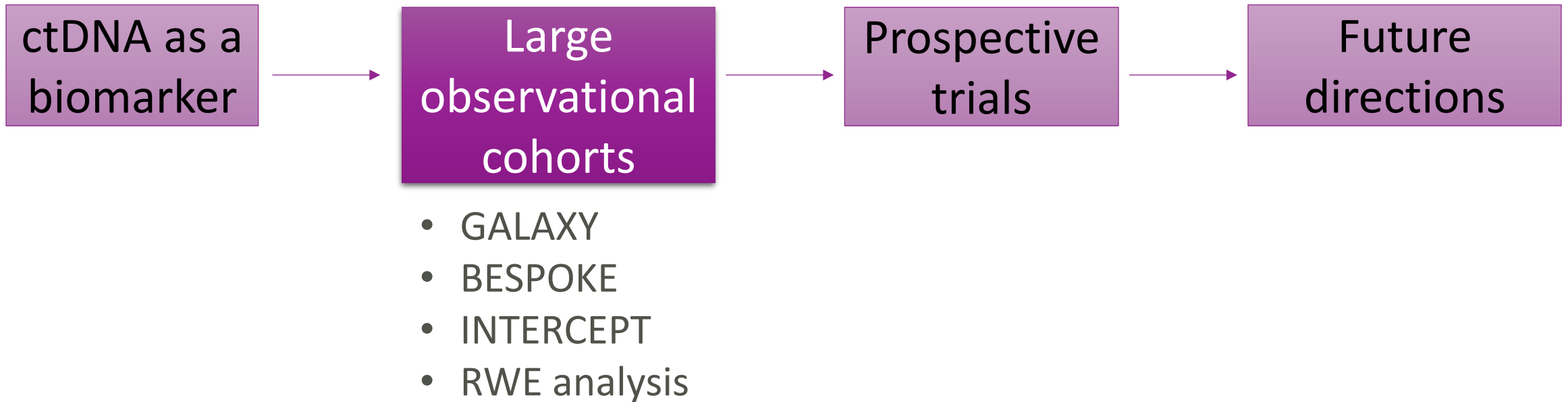
- Detection is cancer tumor burden dependent
- Longitudinal testing can overcome extremely low-level disease → increased sensitivity
- Rate of increase (*e.g.*, doubling time) can be informative

# Minimal/molecular residual disease (MRD)

**MRD** = small volume disease not appreciated radiographically or with other clinical measures

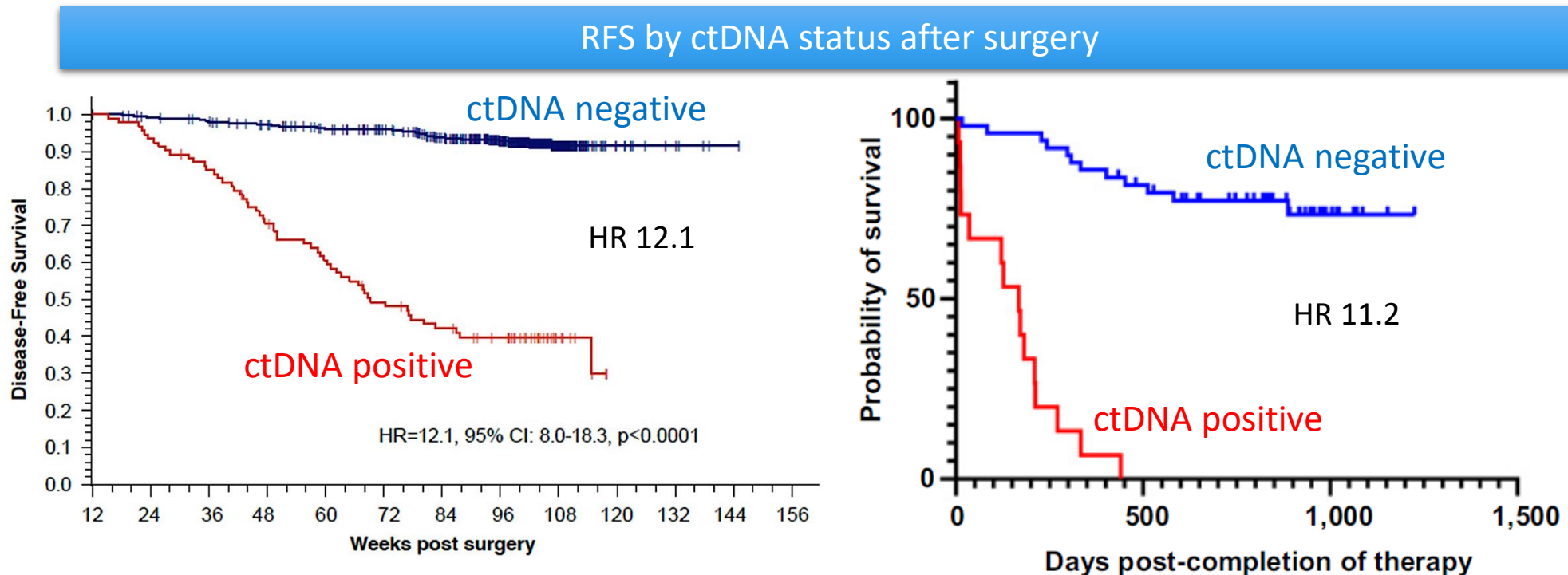
- Hypothesis: ctDNA can pick up recurrences faster than would be detected radiographically or by other blood-based assays (ex. CEA)
- Analyses have largely been retrospective and observational, but with emerging prospective data

# State of the data on ctDNA in colorectal cancer



# ctDNA is a strong prognostic risk factor

- Emerging data with both tumor-informed (LEFT) and tumor-agnostic (RIGHT) platforms

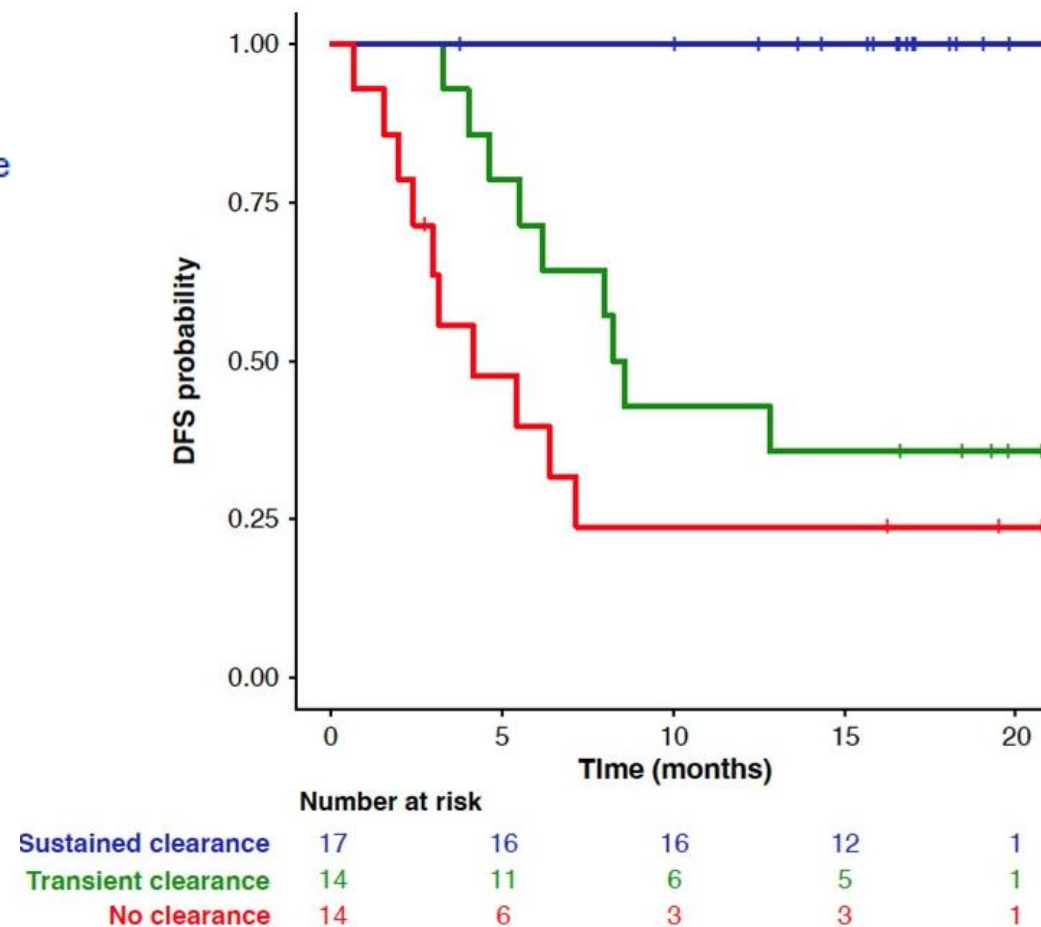
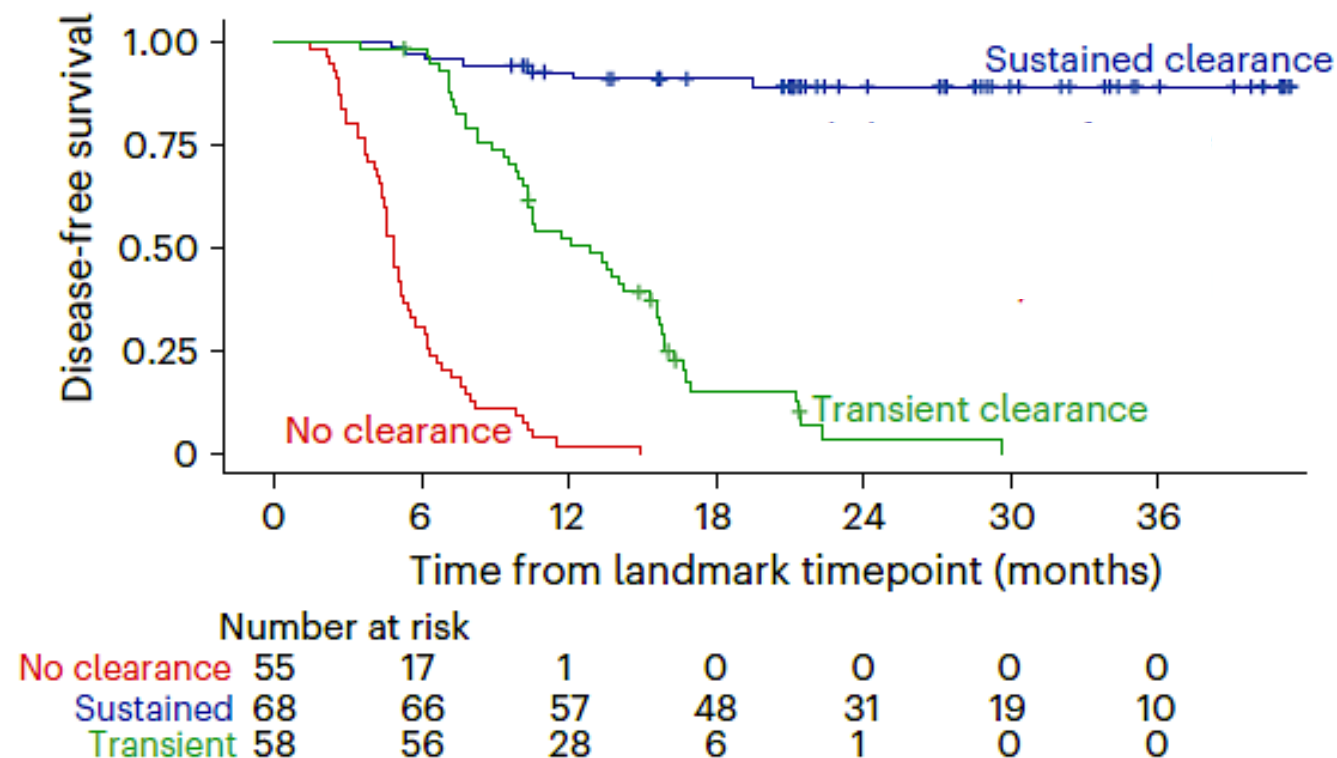


15% ctDNA+; recurrence 60 vs. 7%

18% ctDNA+; recurrence 100 vs. 24%

# Longitudinal ctDNA clearance patterns are prognostic

- GALAXY (Japan) and BESPOKE (USA) studies



# ctDNA+ as a real-time predictor of metastasis

- MDACC INTERCEPT study: n=1115 stage 2-4 with ctDNA evaluation after surgery
  - 184 ctDNA+ during surveillance

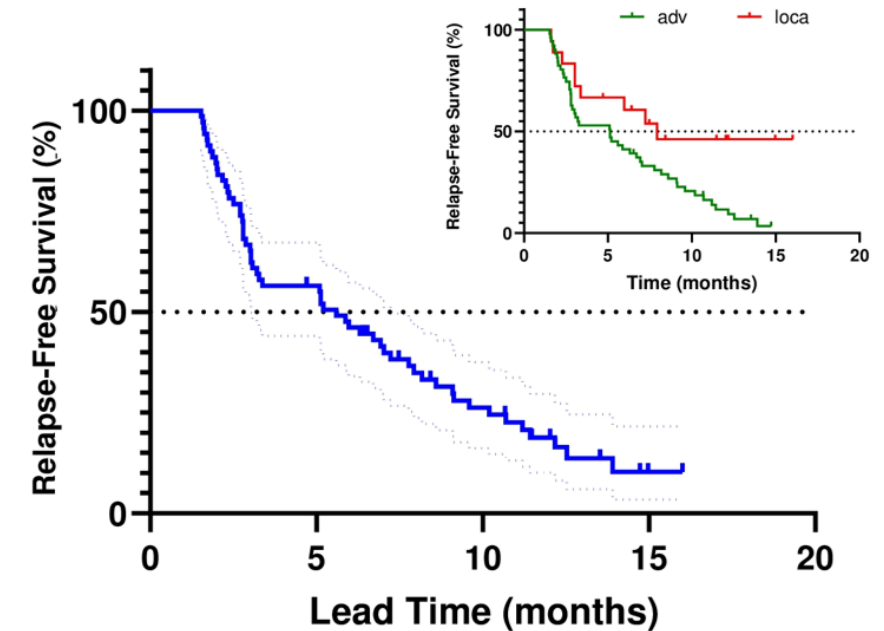
| # of Reflex Investigations   | # of Patients |
|------------------------------|---------------|
| 1                            | 48            |
| 2                            | 18            |
| > 2                          | 7             |
| Type of Reflex Investigation | # of Patients |
| Additional CT                | 25            |
| MRI                          | 21            |
| PET, PET/CT                  | 37            |
| Biopsy                       | 13            |
| Ultrasound                   | 1             |

Radiologic  
evidence of  
metastatic disease

49% n=90

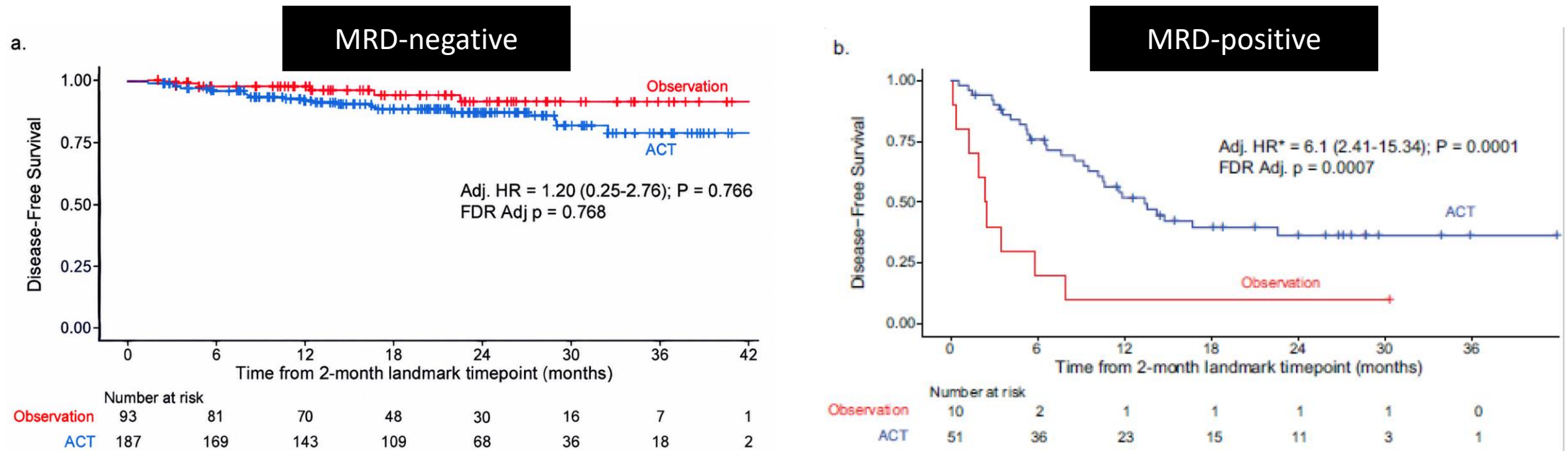
No radiologic  
evidence of  
disease (MRD)  
51% n=94

- Median lead time: 3 mo
  - Excluding concomitant relapse: 5.6 mo

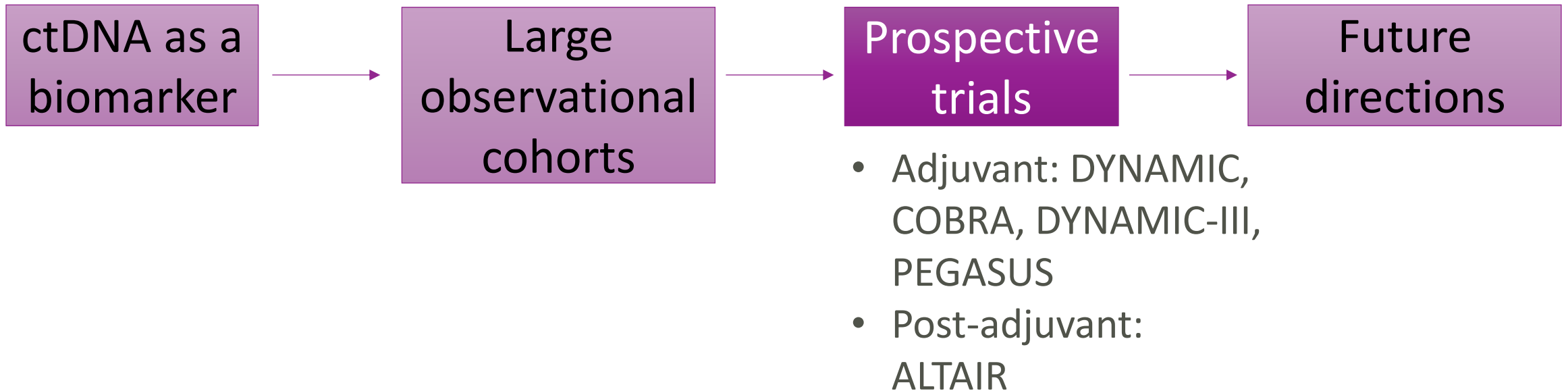


# Real world experience: adjuvant therapy

- Adjuvant therapy has a greater impact on MRD+ in high-risk stage II or stage III

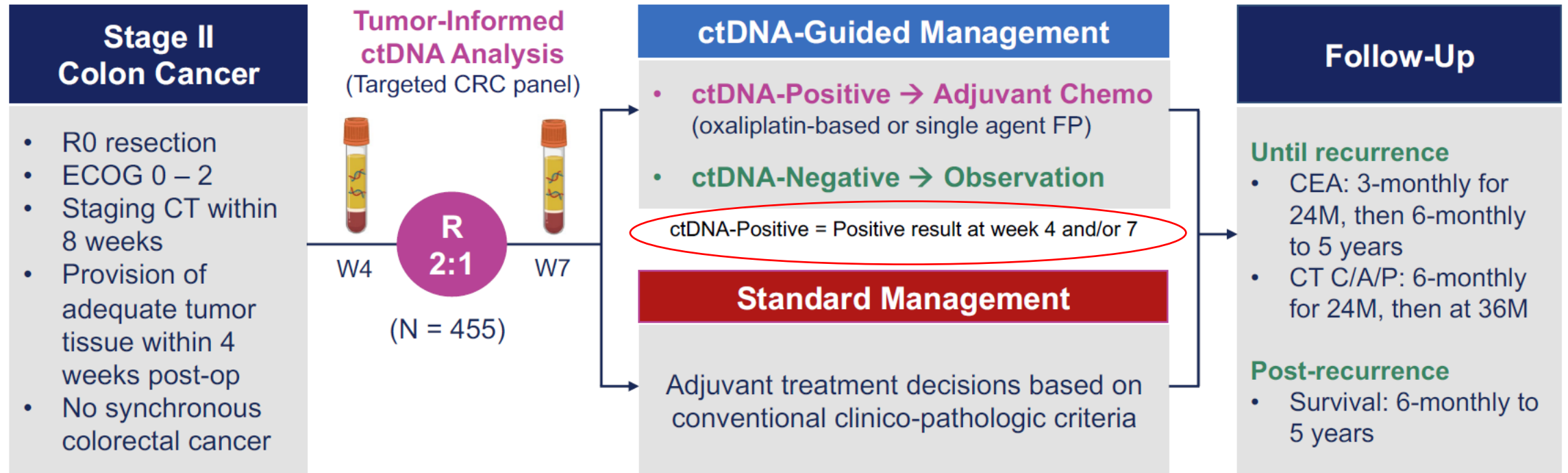


# State of the data on ctDNA in colorectal cancer



# DYNAMIC study

- Prospective study randomizing resected stage II colon cancer 2:1 to ctDNA-guided management

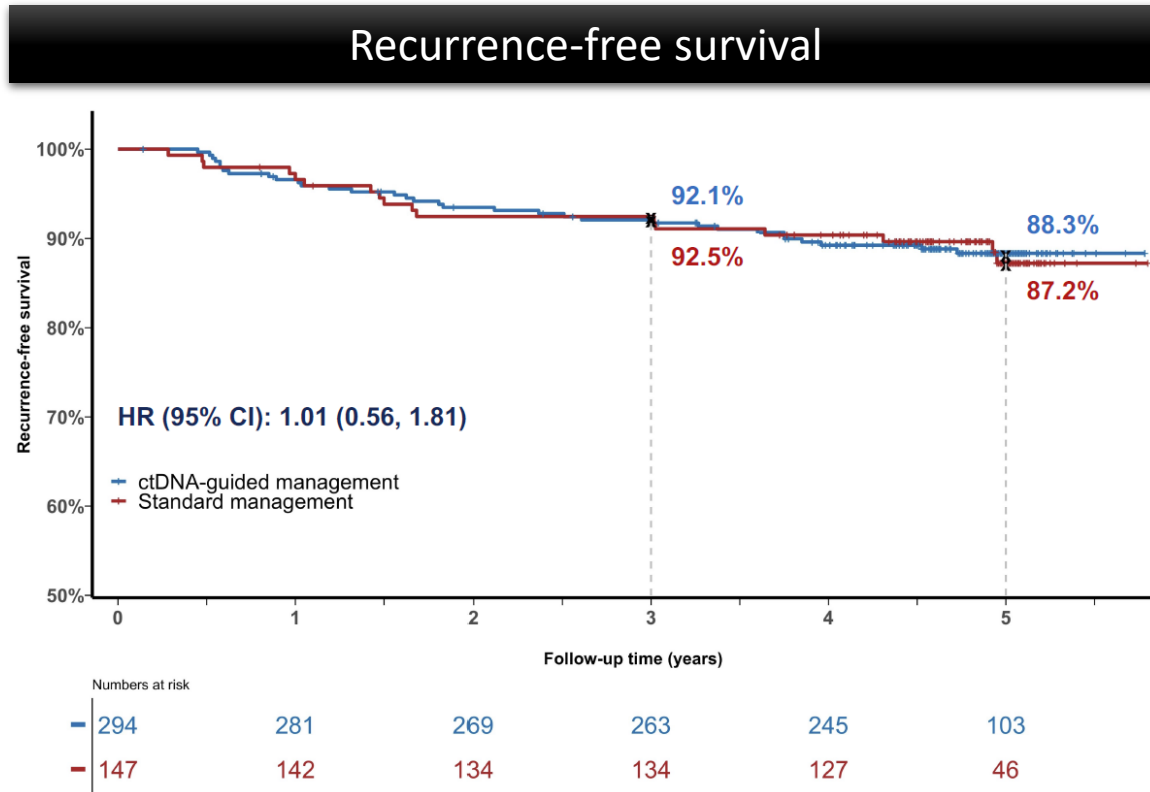


40% were clinical high risk  
20% were MSI-H

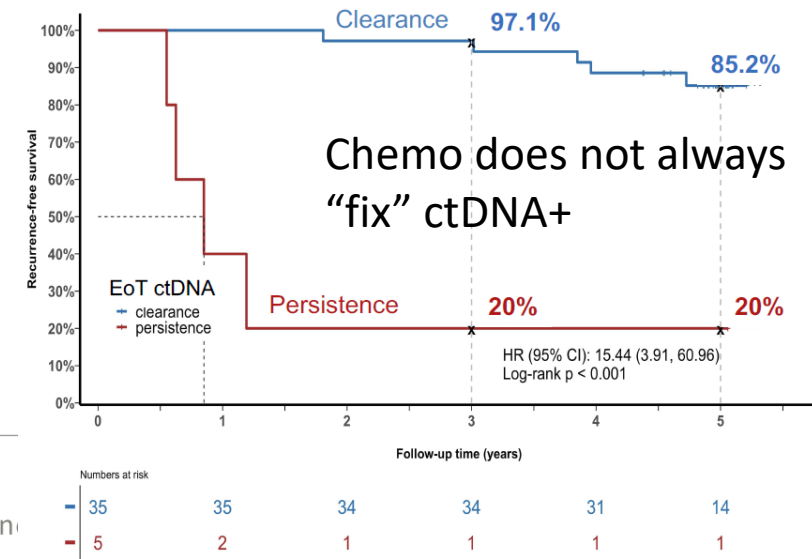
Tie, ASCO 2024; Tie, *New Engl J Med* 2022

# DYNAMIC: recurrence-free survival

- Non-inferior outcomes, despite differences in chemotherapy receipt



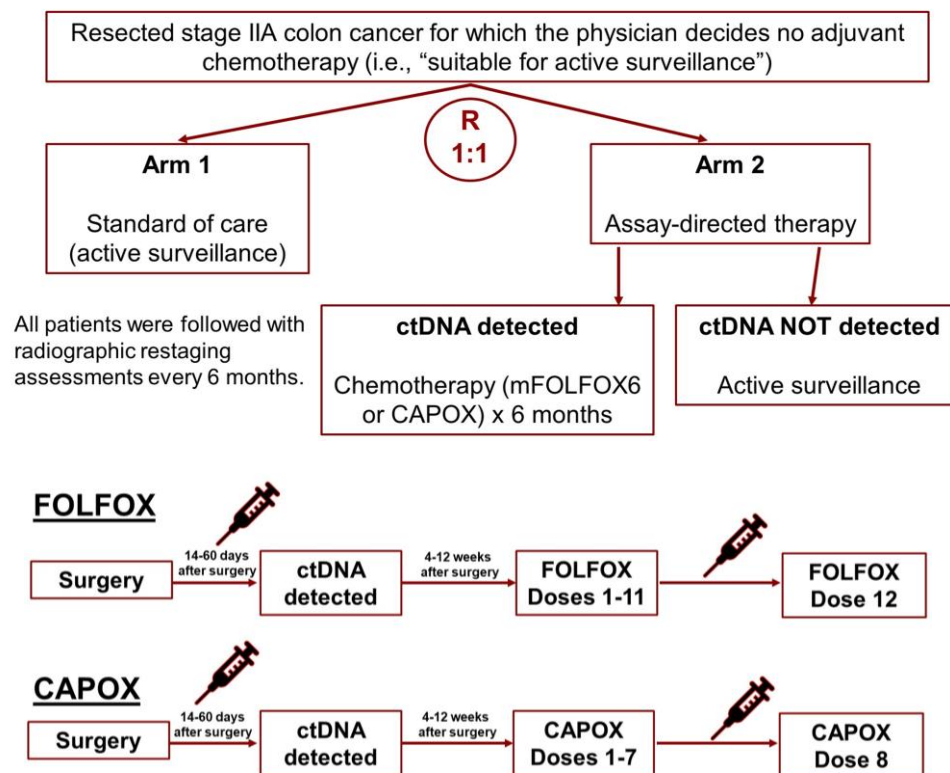
| Treatment Information                | ctDNA-Guided<br>N = 294 | Standard<br>Management<br>N = 147 | P-<br>value |
|--------------------------------------|-------------------------|-----------------------------------|-------------|
| Adjuvant Chemotherapy<br>received, n | 45 (15%)                | 41 (28%)                          | 0.0017      |
| Chemotherapy regimen, n              |                         |                                   |             |
| Oxaliplatin-based doublet            | 28/45 (62%)             | 4/41 (10%)                        | <.0001      |
| Single agent FP                      | 17/45 (38%)             | 37/41 (90%)                       |             |



Tie, ASCO 2024; *New Engl J Med* 2022

# COBRA

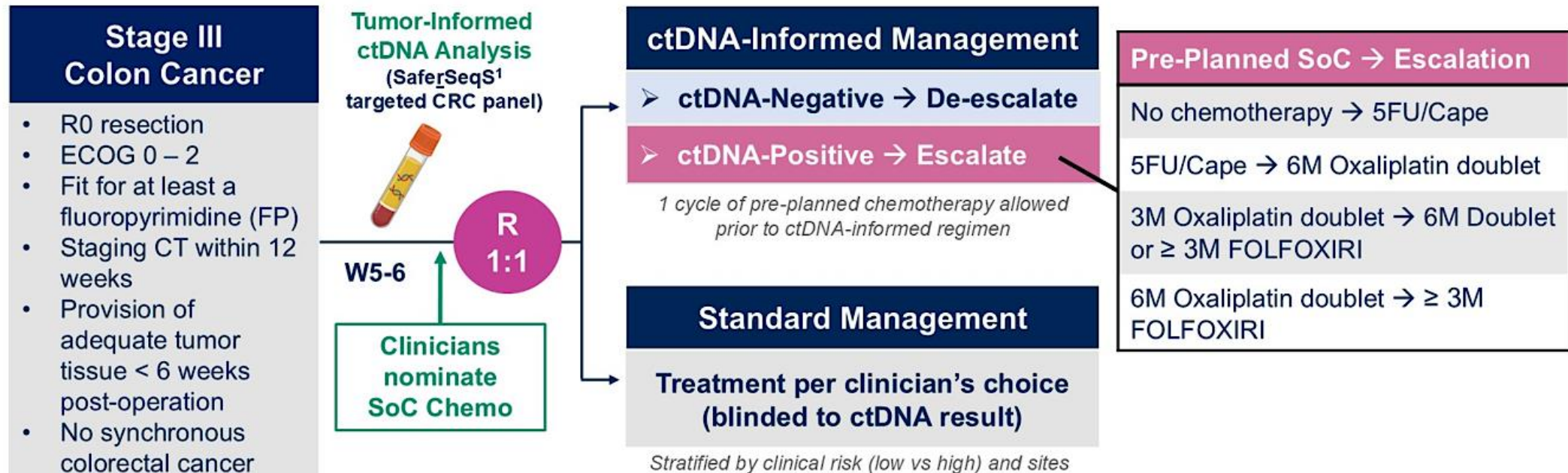
## NRG-GI005 (COBRA) Study Schema



- Stage IIA (T3N0) colon cancer
- Using a (now older) tumor-naïve assay
- 6% ctDNA positive
  - 43% spontaneously cleared in the observation arm (perhaps below the limit of the assay??)
  - 11% cleared in the chemotherapy arm
- Trial stopped early for futility
  - Due to assay issues??

# DYNAMIC-III study

- Prospective study randomizing resected stage III colon cancer 2:1 to ctDNA-guided management



## Primary Analysis of ctDNA-Positive Cohort: Endpoints to be Presented

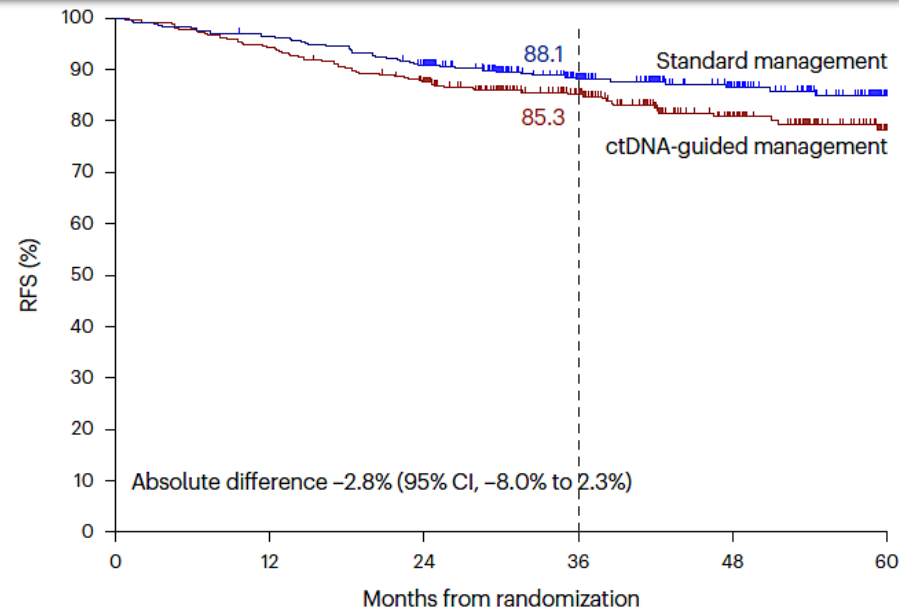
**Primary: 2 years RFS**

**Secondary:** safety, end-of-treatment (EoT) ctDNA clearance

**Exploratory:** post-operative ctDNA levels

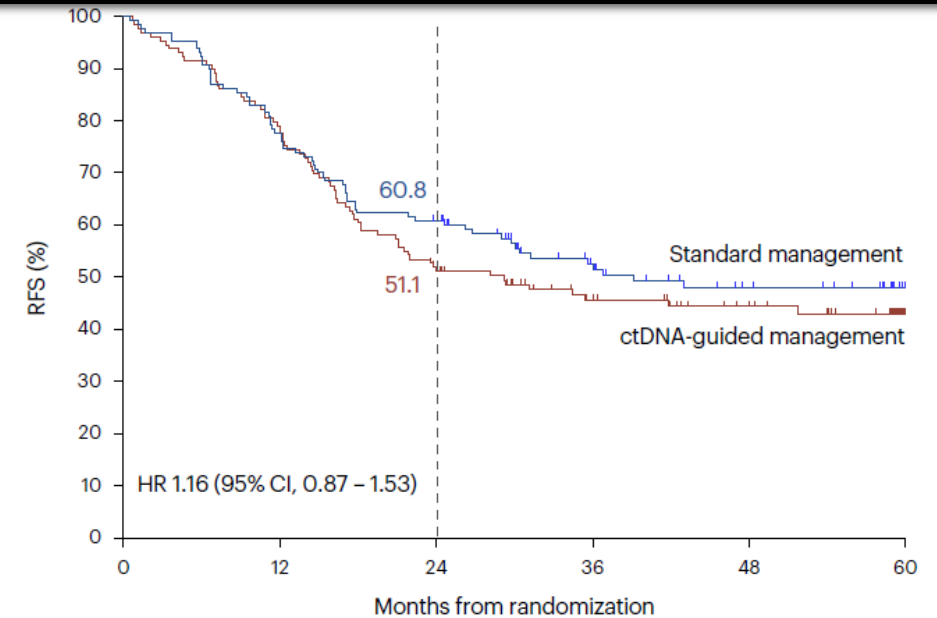
# DYNAMIC-III: Recurrence-free survival

## RFS: ctDNA-negative



|                         |     |     |     |     |     |    |
|-------------------------|-----|-----|-----|-----|-----|----|
| Number at risk          |     |     |     |     |     |    |
| ctDNA-guided management | 353 | 333 | 303 | 214 | 124 | 51 |
| Standard management     | 349 | 336 | 310 | 223 | 143 | 46 |

## RFS: ctDNA-positive

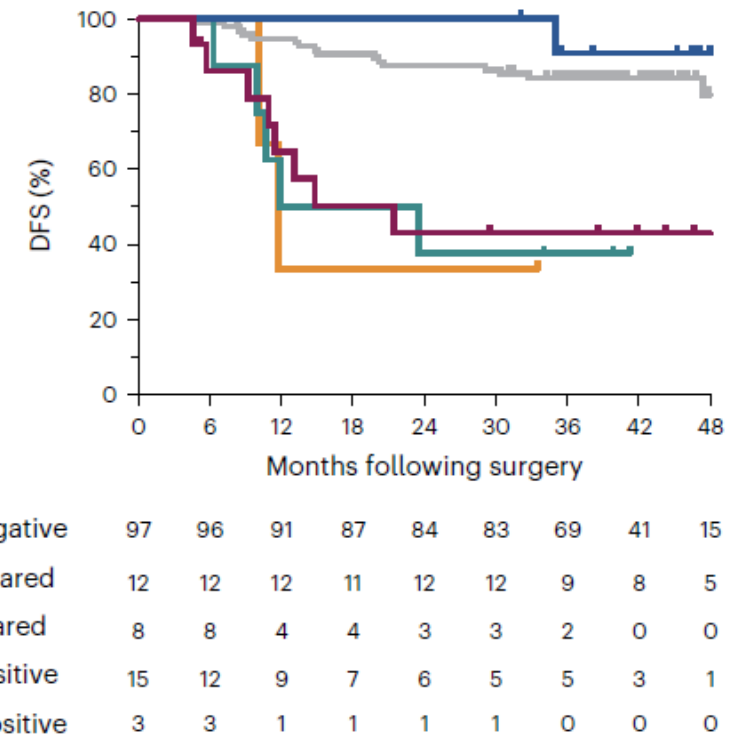
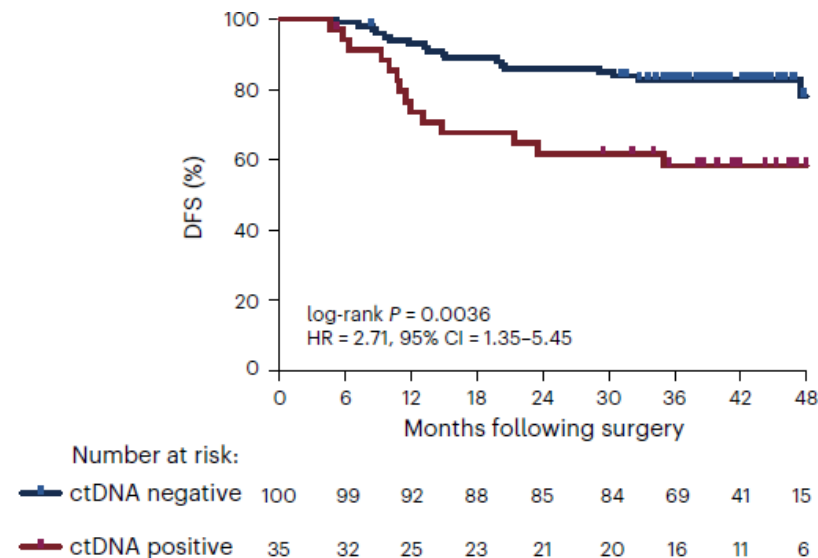


|                         |     |     |    |    |    |    |
|-------------------------|-----|-----|----|----|----|----|
| Number at risk          |     |     |    |    |    |    |
| ctDNA-guided management | 129 | 101 | 64 | 45 | 31 | 7  |
| Standard management     | 130 | 101 | 78 | 49 | 33 | 15 |

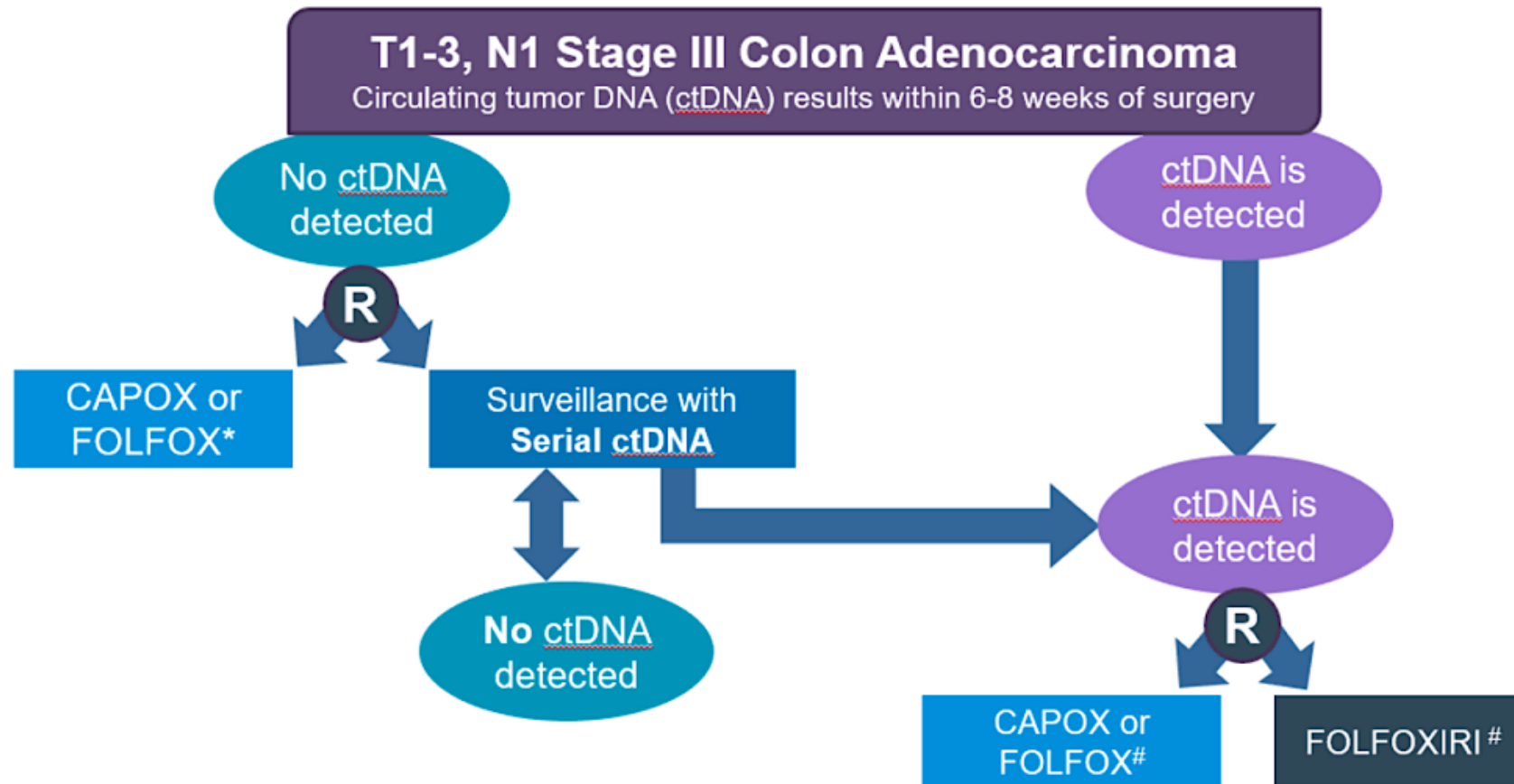
....Is it the assay? Cohort heterogeneity? Specific regimen?

# PEGASUS

- Phase 2 of resected T4N0 and stage III → ctDNA-guided adjuvant therapy
  - ctDNA-: 6 mo capecitabine / ctDNA+: CAPOX x 3 mo
  - After 3 mo: still +: FOLFIRI x6 mo; cleared: cape

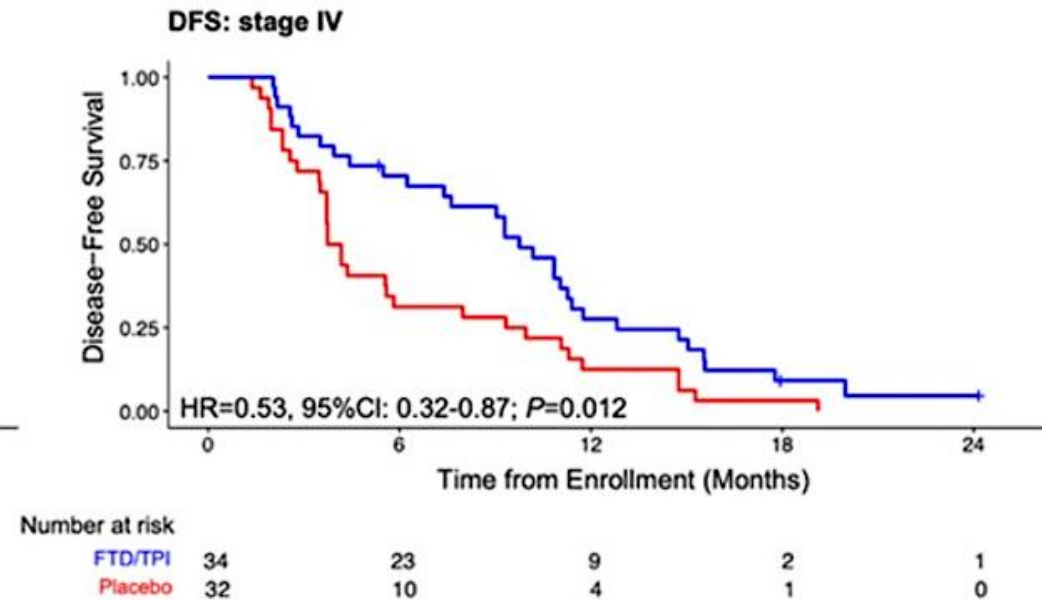
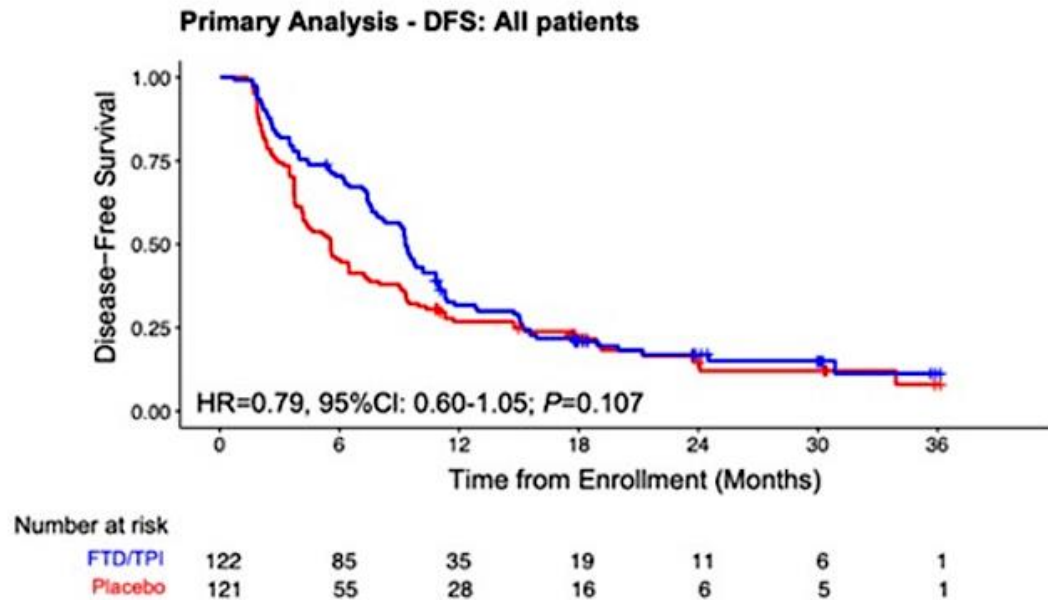
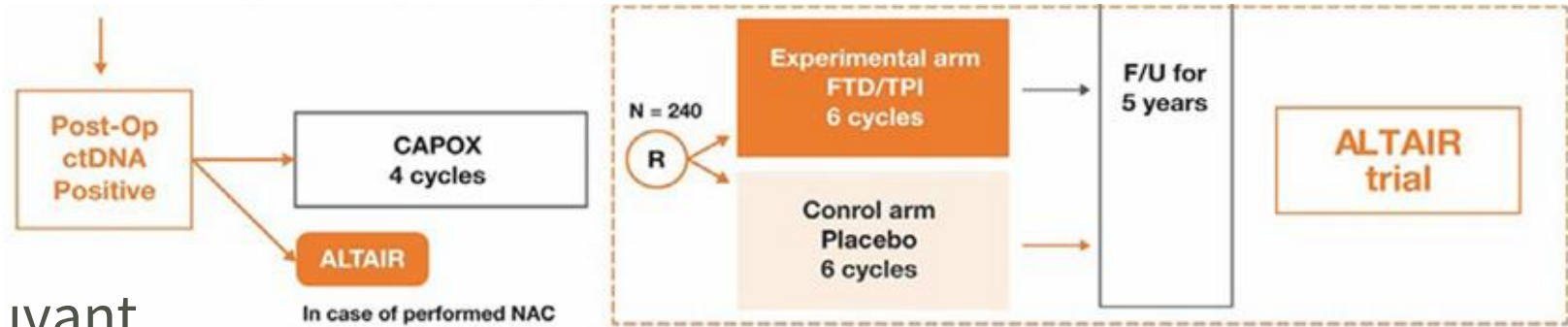


# CIRCULATE-North America



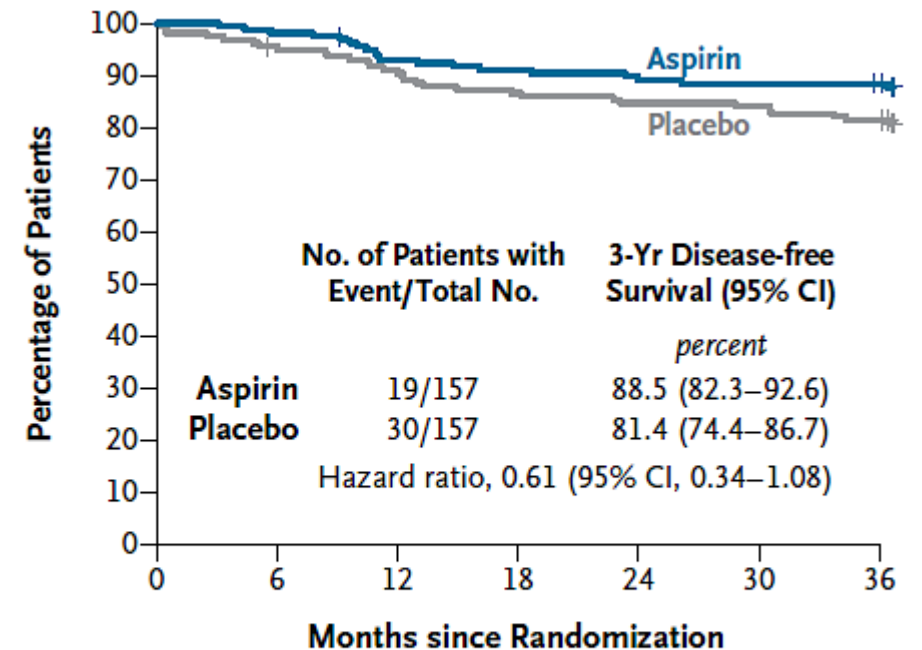
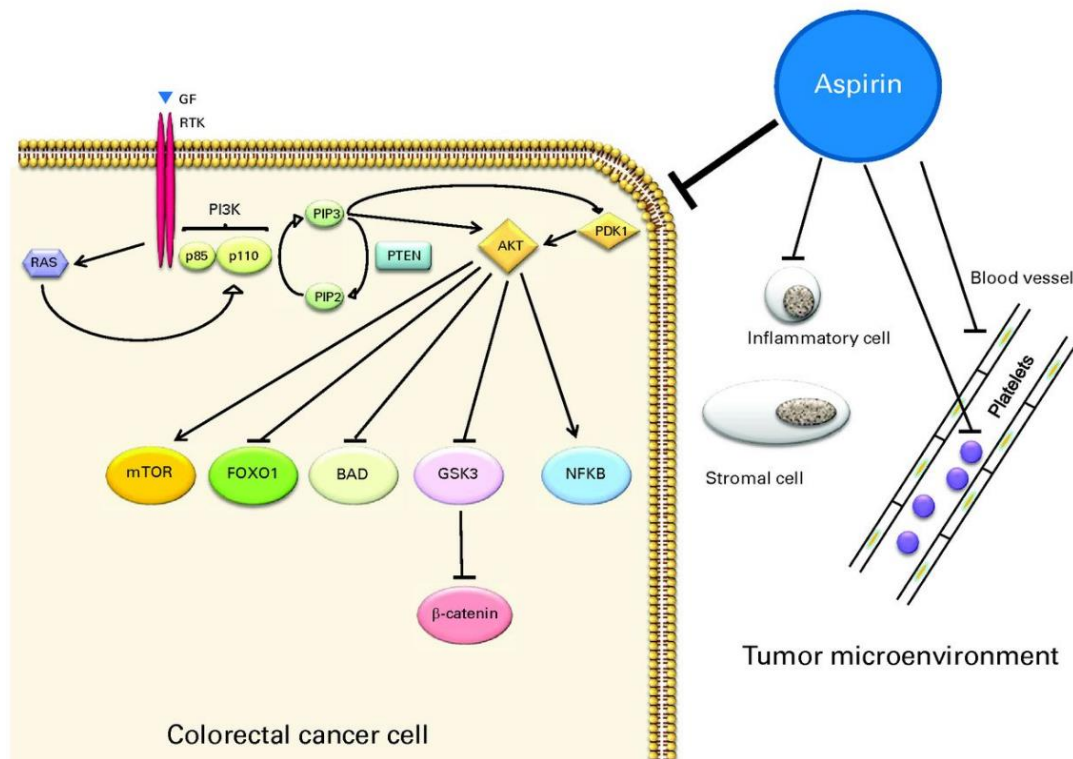
# ALTAIR

- N=243, stage 2-4 post-adjuvant
- 36% had neoadjuvant chemo, 46% had adjuvant



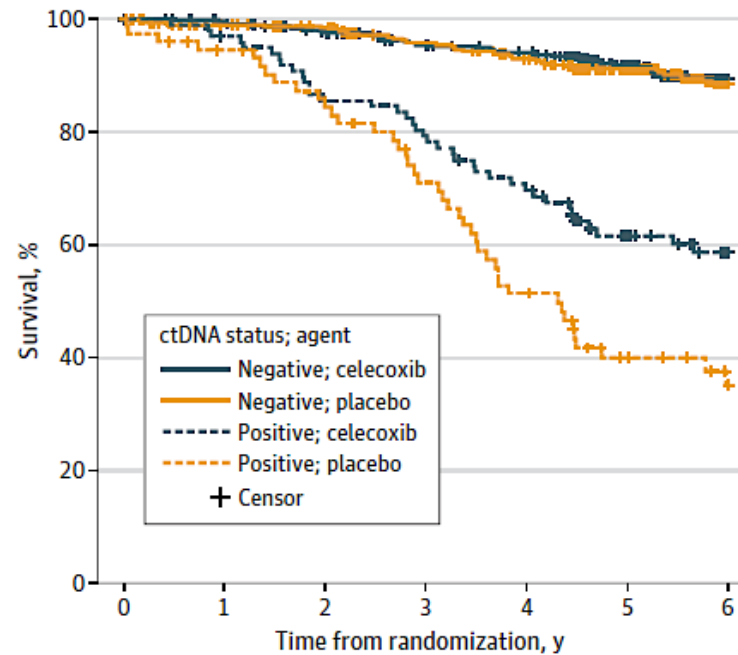
# Exploratory: ALASCCA

- Prospective study of adjuvant 160mg aspirin vs placebo x 3 years for localized PI3Kmut CRC



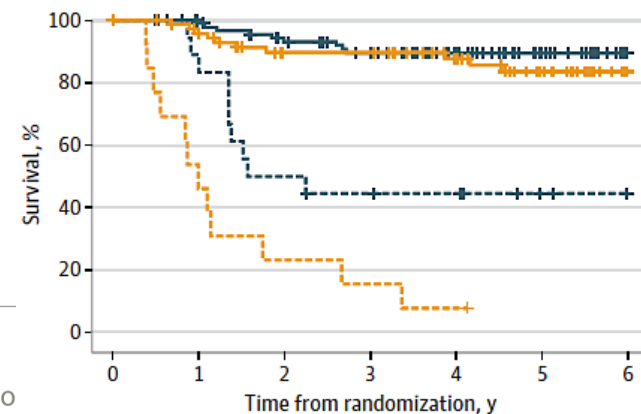
| No. at Risk |     |     |     |     |     |     |     |
|-------------|-----|-----|-----|-----|-----|-----|-----|
| Aspirin     | 157 | 155 | 146 | 143 | 140 | 139 | 138 |
| Placebo     | 157 | 150 | 142 | 136 | 133 | 132 | 128 |

# Exploratory: CALGB/SWOG 80702



|                     |     |     |     |     |     |     |     |
|---------------------|-----|-----|-----|-----|-----|-----|-----|
| No. at risk         |     |     |     |     |     |     |     |
| Negative, celecoxib | 375 | 361 | 344 | 327 | 317 | 266 | 168 |
| Negative, placebo   | 392 | 372 | 359 | 340 | 323 | 269 | 155 |
| Positive, celecoxib | 99  | 94  | 82  | 75  | 65  | 47  | 32  |
| Positive, placebo   | 74  | 67  | 59  | 47  | 34  | 21  | 14  |

- Post-hoc analysis of this stage 3 trial
  - 2x2 randomization to 3 vs 6 mo chemotherapy & 3 yrs of celecoxib or placebo
- ctDNA+ associated with poor prognosis
- Celecoxib benefit greatest in ctDNA+ patients, even when restricting to PIK3CA-mut (22%)

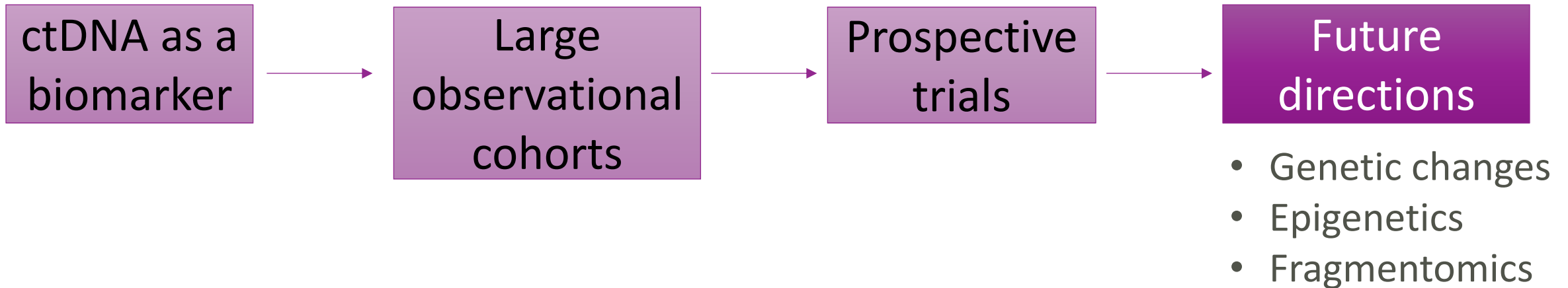


Nowak, *GI ASCO* 2025; Zhang, *JAMA Oncol* 2025

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# State of the data on ctDNA in colorectal cancer



# ctDNA is not static, it is a technology

- Ongoing and future developments
  - Discrete number of variants per patient (e.g., 16) → increased panel sizes
  - Depth and breadth of sequencing (Whole exome → whole genome)
  - Inclusion/improvement of epigenetics
  - Especially relevant for tumor-agnostic assays
  - Better cancellation of background “noise” (e.g., CHiP)
  - Binary reporting (positive/negative) → quantitative trending → evaluations of fold differences as a biomarker

# Case scenario: stage II colon cancer



41yo woman presents with rectal bleeding

- Colonoscopy: ulcerated, fungating mass in the sigmoid colon.
  - Biopsy: invasive, moderately differentiated adenocarcinoma
- CT CAP: no evidence of metastatic disease
- Oncologic resection: **T3N0**. 4.2cm moderately differentiated adenocarcinoma
  - No evidence of lymphovascular or perineural invasion. Low tumor budding. Negative margins.
  - 0/16 lymph nodes with cancer, no tumor deposits.
  - Microsatellite stable (MSS) by next generation sequencing

Low-risk stage II colon cancer

Typically, would observe (no  
adjuvant chemotherapy)

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  - 0/16 lymph nodes with cancer, no tumor deposits.
  - Microsatellite stable (MSS) by next generation sequencing
- This patient elected ctDNA testing after surgery
- The draw from 21 days after surgery was **POSITIVE** (0.5 MTM/ml)

Strongly consider giving adjuvant chemotherapy

I personally would give an oxaliplatin doublet for ctDNA+

# Case scenario: stage III colon cancer

41yo woman presents with rectal bleeding

- Colonoscopy: ulcerated, fungating mass in the sigmoid colon.
  - Biopsy: invasive, moderately differentiated adenocarcinoma
- CT CAP: no evidence of metastatic disease
- Oncologic resection: **T3N1**. 4.2cm moderately differentiated adenocarcinoma
  - No evidence of lymphovascular or perineural invasion. Low tumor budding. Negative margins.
  - 3/16 lymph nodes positive, no tumor deposits.
  - Microsatellite stable (MSS) by next generation sequencing



Low-risk stage III colon cancer

Recommend 3 months of  
adjuvant chemotherapy

# Case scenario: stage III colon cancer



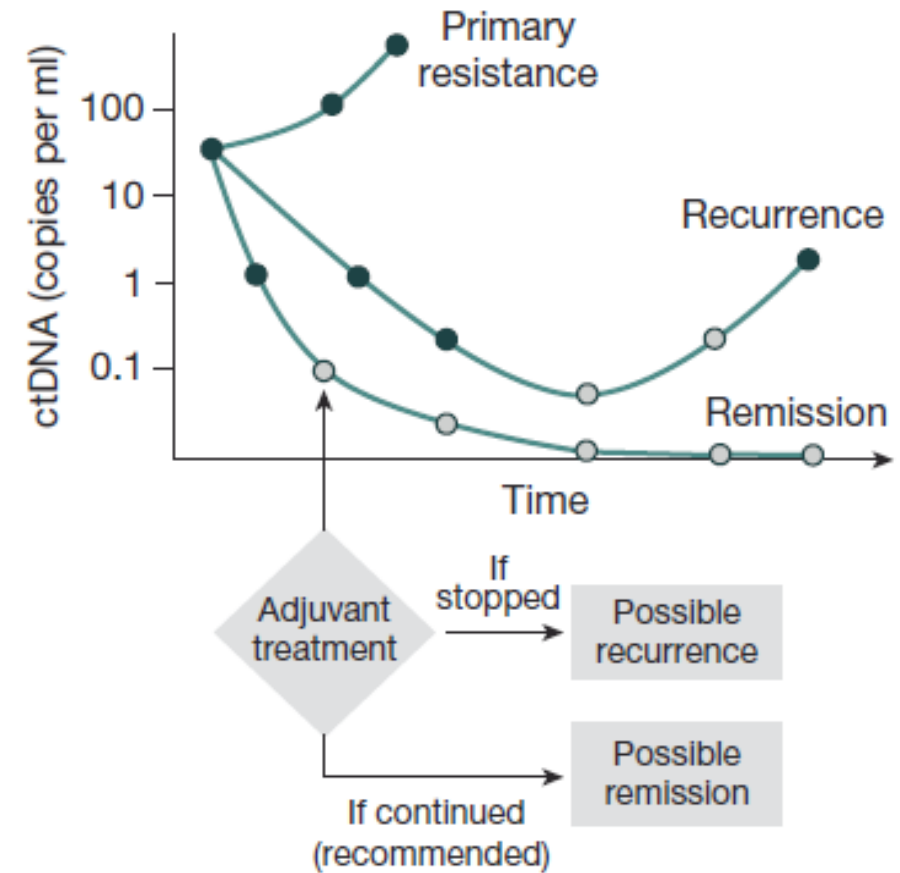
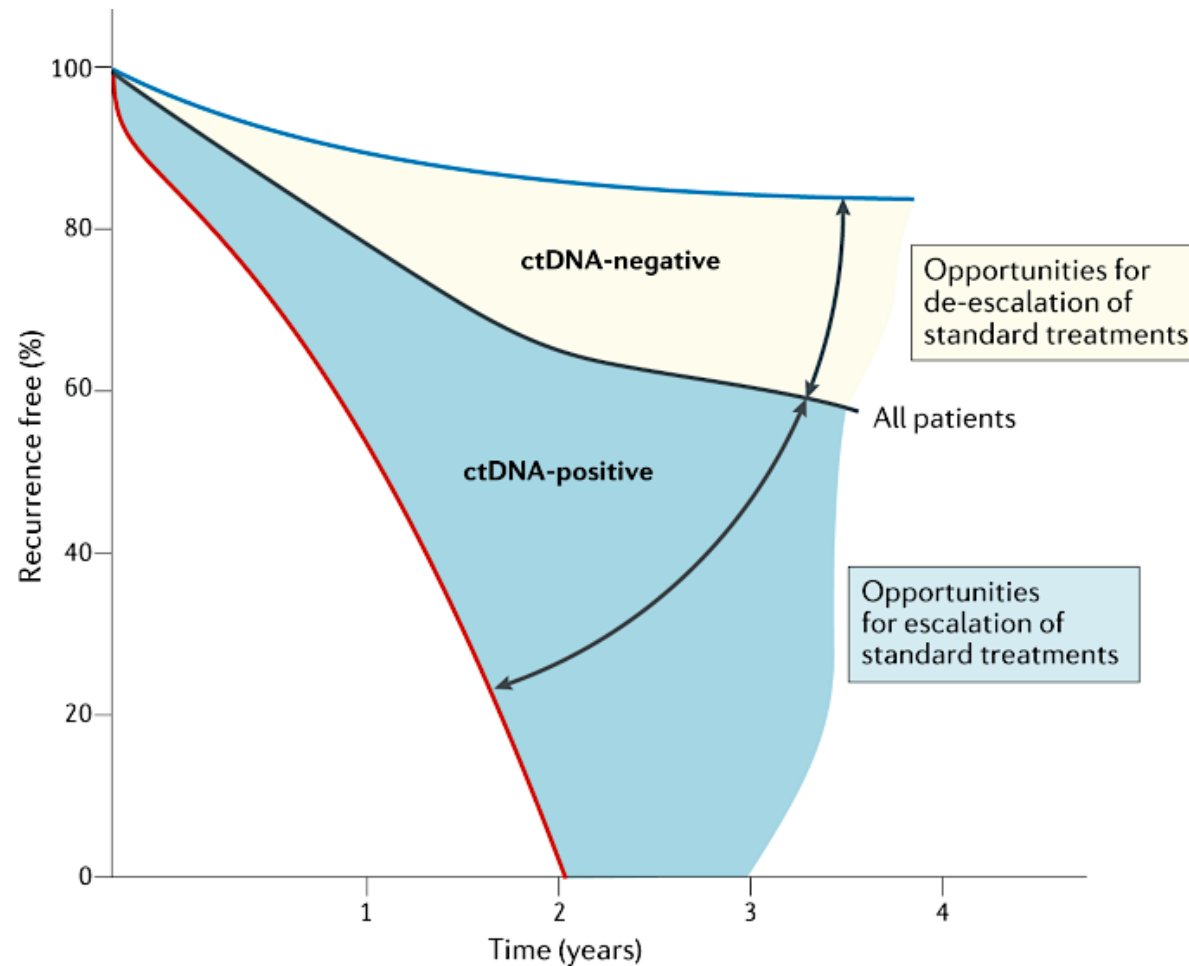
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  - No evidence of lymphovascular or perineural invasion. Low tumor budding. Negative margins.
  - 3/16 lymph nodes positive, no tumor deposits.
  - Microsatellite stable (MSS) by next generation sequencing
- This patient elected ctDNA testing after surgery
- The draw from 21 days after surgery resulted as **NEGATIVE**

Still give 3 months of adjuvant chemotherapy

Low threshold to de-escalate or stop for toxicity

# Is ctDNA the future? Most likely in some capacity



Dasari, *Nat Rev Clin Oncol* 2020; Cohen, *Nature* 2023

# Thank you!



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