From sample to treatment – Clinical applications

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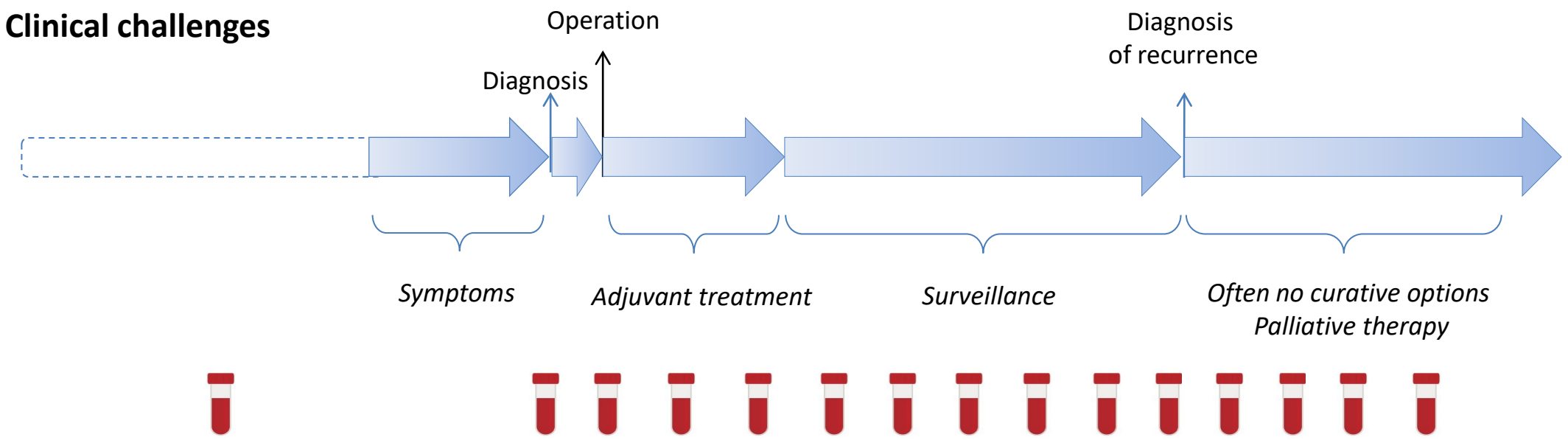
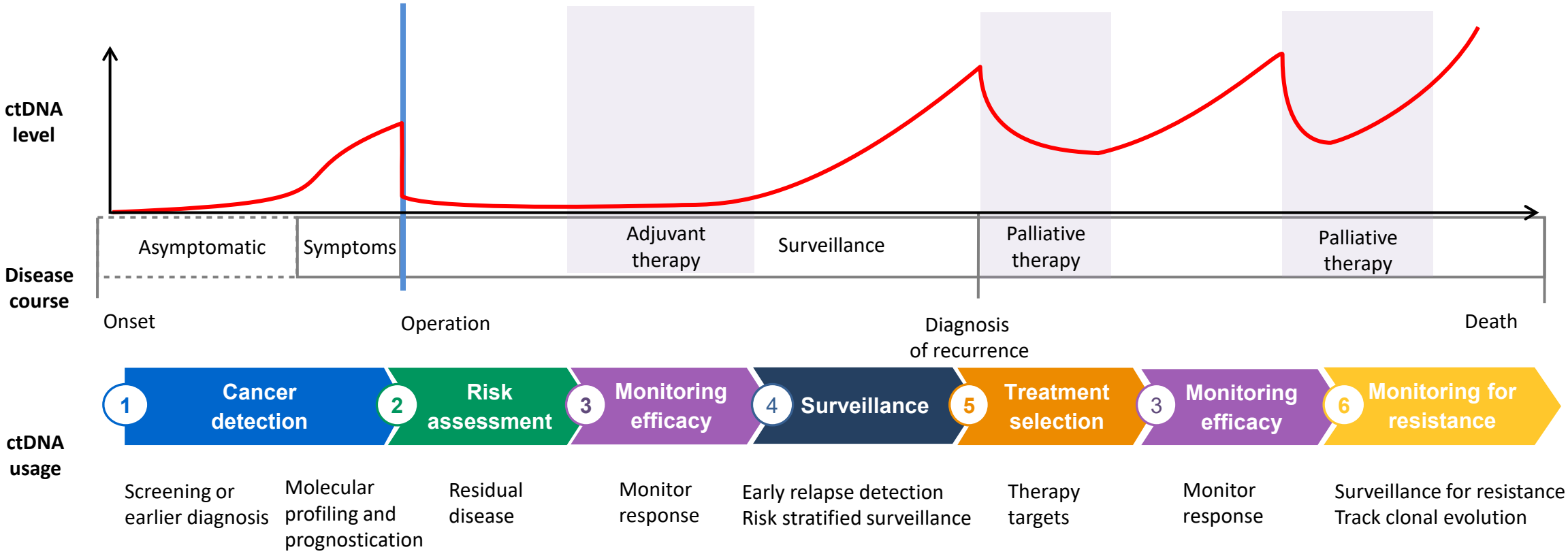
ctDNA has potential to be used throughout the disease course



ctDNA analysis

- Minimally Invasive, minimal risk, nearly always available
- Enables cancer detection and quantification of cancer burden
- Biological information/insights about cancer biology and evolution

ctDNA has potential to be used throughout the disease course



ctDNA advancements offer many patient benefits

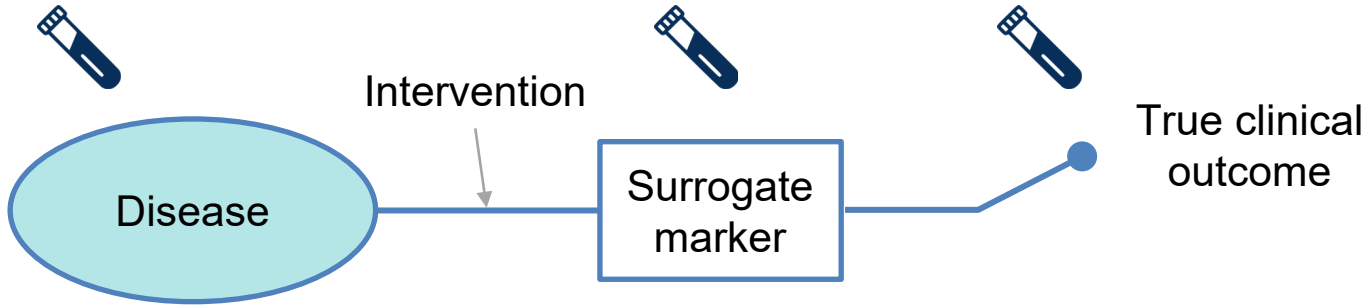
1 Cancer detection | 2 Risk determination | 3 Monitoring efficacy | 4 Surveillance | 5 Treatment selection | 3 Monitoring efficacy | 6 Monitoring for resistance

Patient benefits

- Less invasive alternative to follow-up tissue biopsies
- Allows for earlier detection of cancer and recurrence *(and may improve outcomes)*
- Allows for earlier and more frequent monitoring of treatment effectiveness
- Removes barriers for more frequent testing of mutation status
- Enables risk adapted therapy

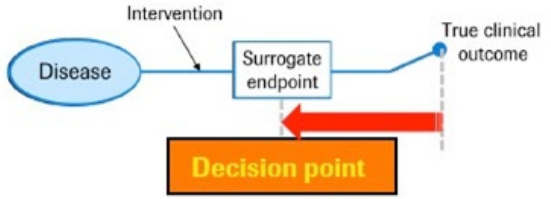
Application for ctDNA as a potential surrogate marker for clinical outcome: drug development impact

Surrogate endpoints shorten drug development/clinical trial timelines and lead to faster filing decision and launch out to patients



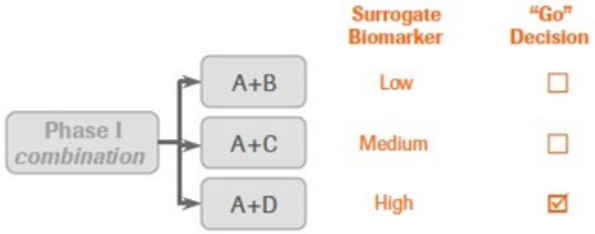
Opportunities

Accelerate development



Earlier decision making / risk assessment

Combination selection

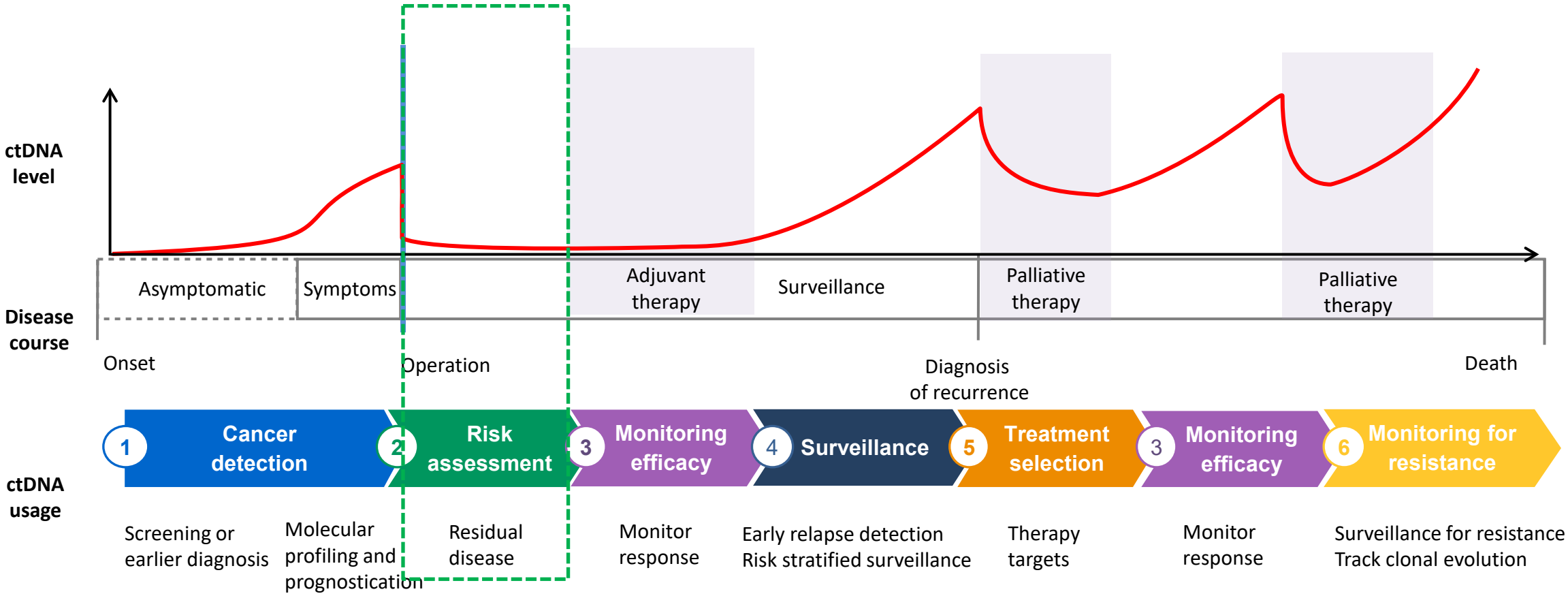


Risk stratification to inform combination approaches

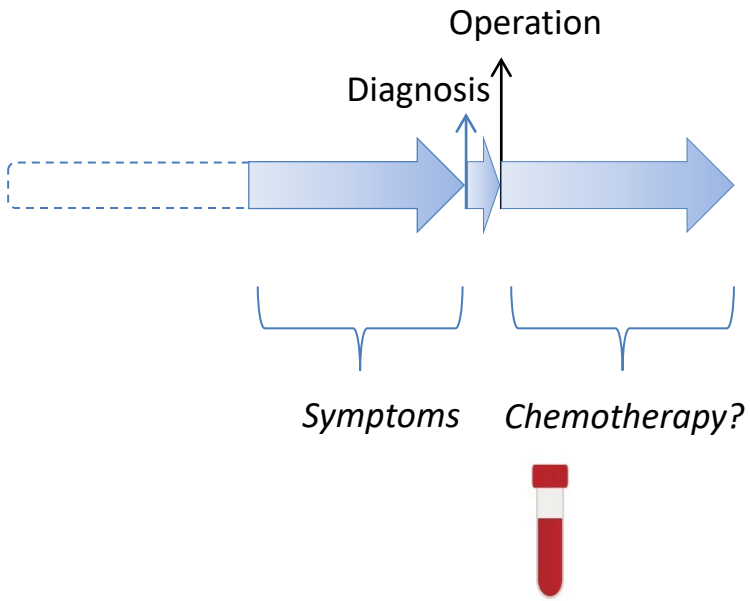
Optimise treatment

Risk stratification of patients with Stable Disease (SD)

ctDNA has potential to be used throughout the disease course



Can ctDNA analysis identify the patients in need of adjuvant chemotherapy?

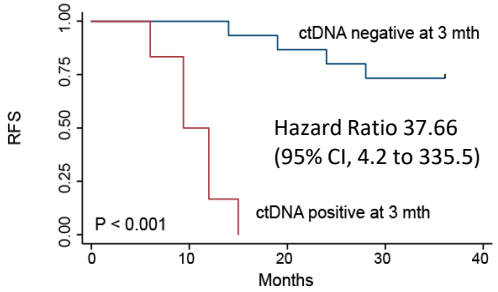


Clinical challenge:

Who is at risk of relapsing ?

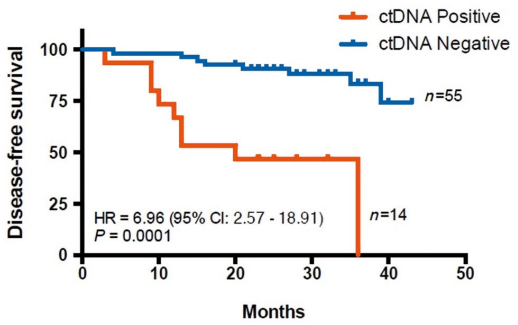
Can ctDNA detect post-operative residual disease?

Stage I-III
(no ACT)



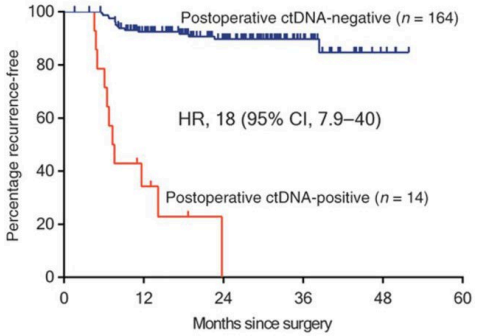
Schøler et al.,
Clin Cancer Res. Jun 9, 2017

Stage I-III
(+/- ACT)



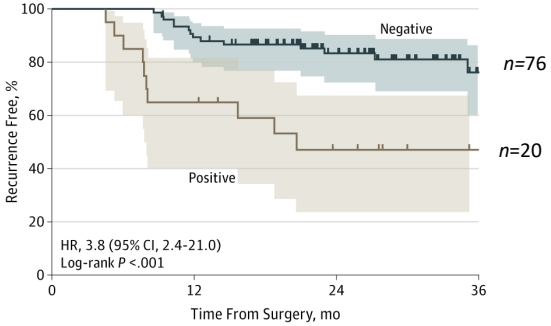
Tarazona et al
Annals of Oncology, sep, 2019

Stage II
(no ACT)



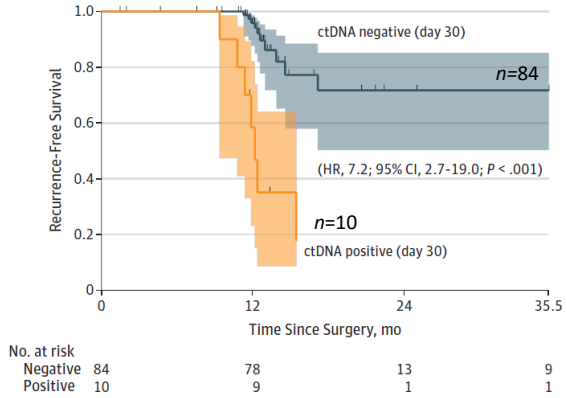
Tie et al.,
Sci Transl Med 2016

Stage III
(+ ACT)



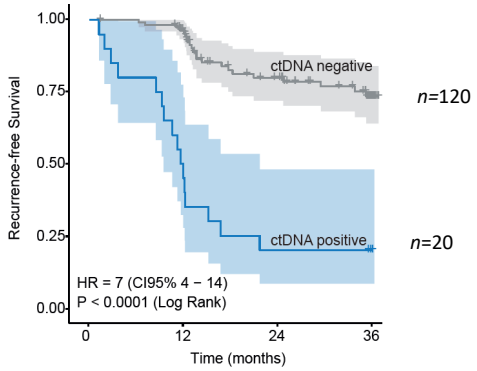
Tie et al.,
JAMA Oncol, Oct, 2019

Stage I-III
(+/- ACT)



Reinert et al.,
JAMA Oncol, Aug, 2019

Stage III
(+ ACT)



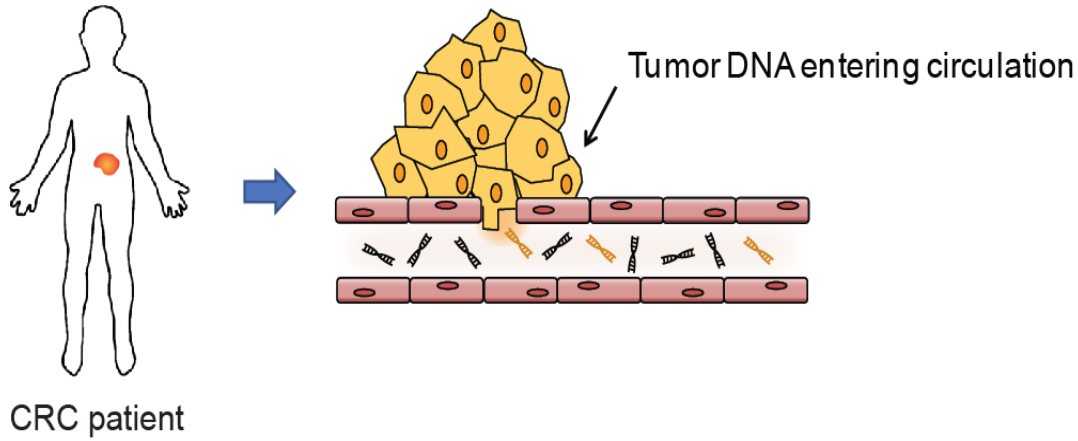
Henriksen et al.,
Clin Cancer Res. Oct 8, 2021

Clinical implication

PostOP ctDNA positive

Microscopic residual disease

Can escalation save lives ?



Trial Name/Country	Patient Population	Sample Size	ctDNA Assay	Timing of ctDNA Testing	Trial Intervention	Primary Objective
ctDNA-Guided Strategy Design						
DYNAMIC (ACTRN-12615000381583) Australia	Stage II colon cancer	450	Safe-SeqS	Week 4 and 7 post-op	**Standard of care:** clinician determined management (surveillance or adjuvant chemotherapy) based on standard clinicopathological features **ctDNA-guided:** ctDNA-positive → adjuvant chemotherapy; ctDNA-negative → surveillance	To demonstrate that an adjuvant therapy strategy based on post-op ctDNA results will reduce the number of patients receiving adjuvant chemotherapy without compromising recurrence-free survival
MEDOCC-CrEATE (NL6281/NTR6455) [80] Netherlands	Stage II colon cancer	1320	PGDx elio™	4–21 days post-op	**Standard of care:** surveillance **ctDNA-guided:** ctDNA-positive → 6 months of CAPOX; ctDNA-negative → surveillance	To investigate the willingness of patients to receive adjuvant chemotherapy after detection of ctDNA post-surgery
NRG GI-005 (COBRA) NCT04068103 [81] United States/Canada	Stage IIA colon cancer	1408	Guardant LUNAR-1™	Post-op	**Standard of care:** Surveillance **ctDNA-guided:** ctDNA-positive → adjuvant FOLFOX/CAPOX; ctDNA-negative → surveillance	• To compare the clearance of ctDNA between arms for the baseline ctDNA-positive patient at 6 months (phase II) • To compare median RFS between arms for the baseline ctDNA-positive patients at 6 months (phase III)
CIRCULATE AIO-KRK-0217 (NCT04089631) [82] Germany	Stage II colon cancer (MSS tumours)	4812	Not reported	Post-op	ctDNA-positive patients randomised to: **Standard of care:** surveillance **Experimental:** adjuvant chemotherapy (capecitabine or CAPOX)	To compare the disease-free survival in patients who are positive for postoperative ctDNA treated with or without adjuvant chemotherapy
CIRCULATE PRODIGE 70 (NCT04120701) [83] France	Stage II colon cancer	1980	ddPCR (2 methylated markers WIF1 and NPY)	Week 2–8 post-op	198 ctDNA-positive patients randomised to: **Standard of care:** surveillance **Experimental:** adjuvant FOLFOX	To demonstrate a 17.5% gain in 3-year DFS in post-op ctDNA-positive patients treated with adjuvant FOLFOX compared to observation alone

Clinical implication

PostOP ctDNA negative

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No microscopic residual disease

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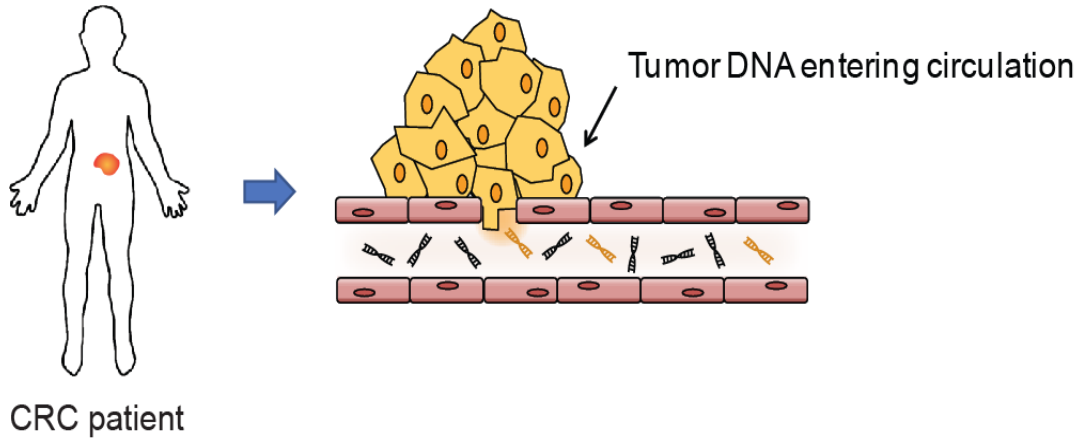
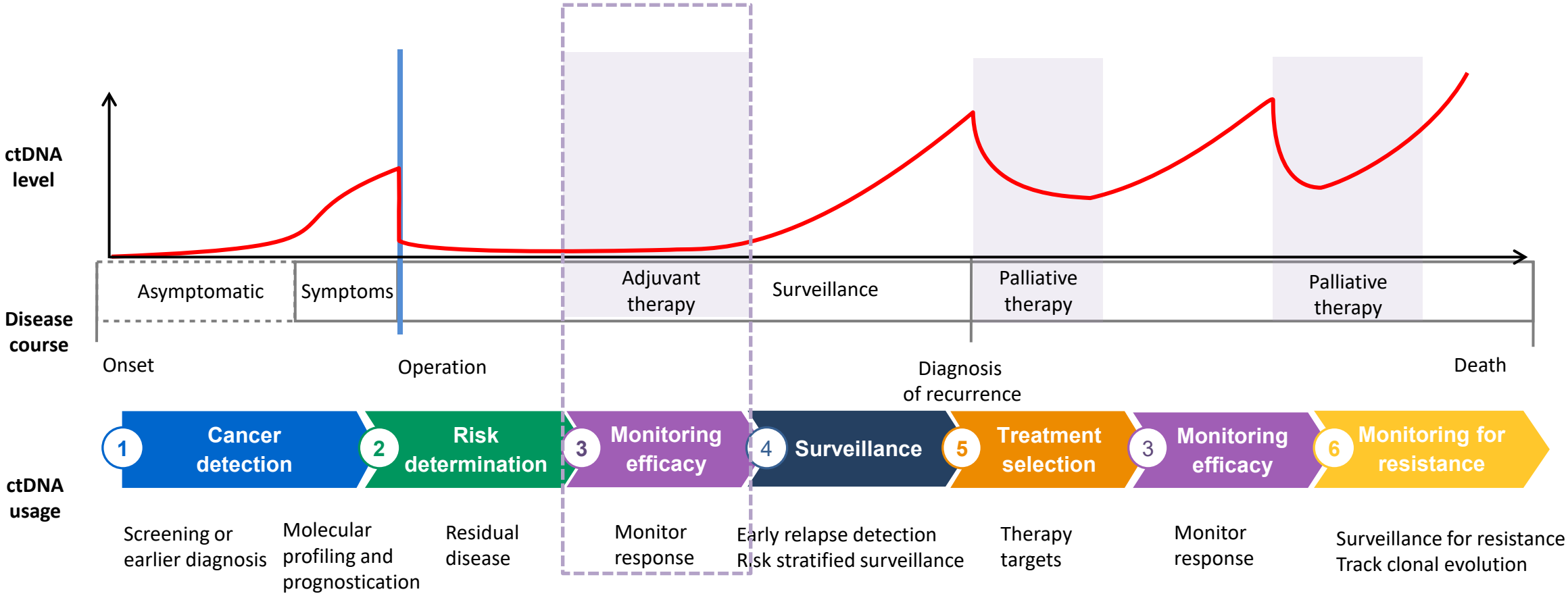
Can we de-escalate and avoid toxicity?

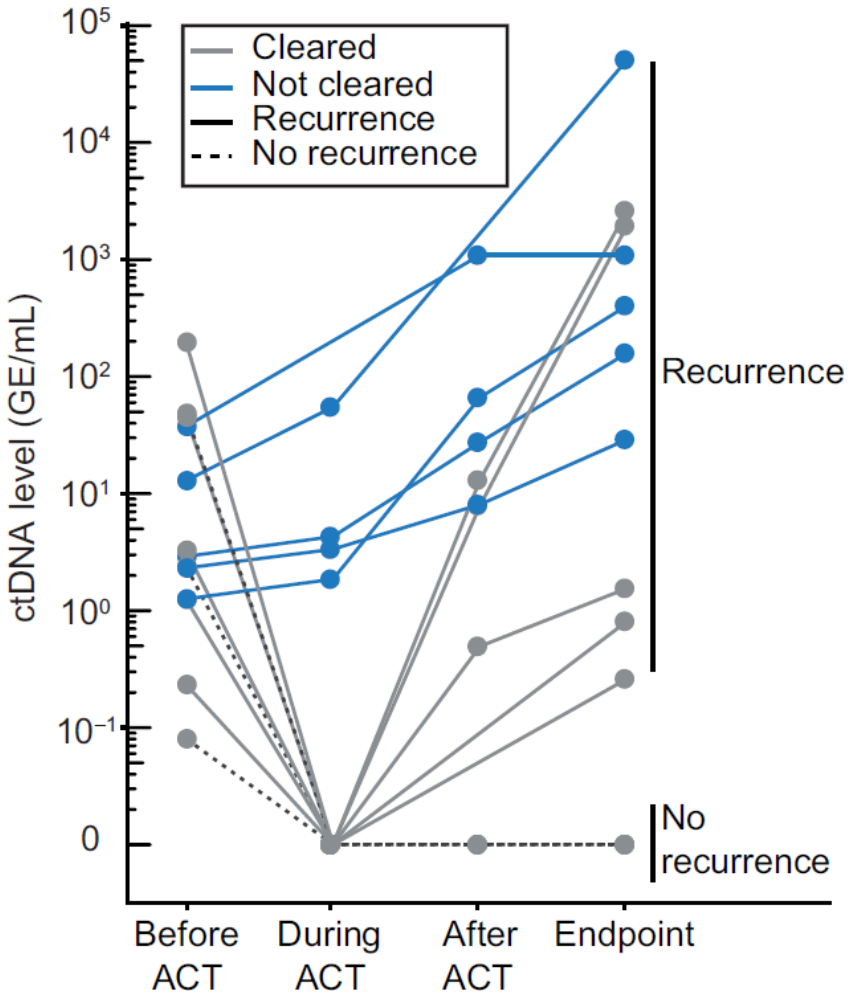


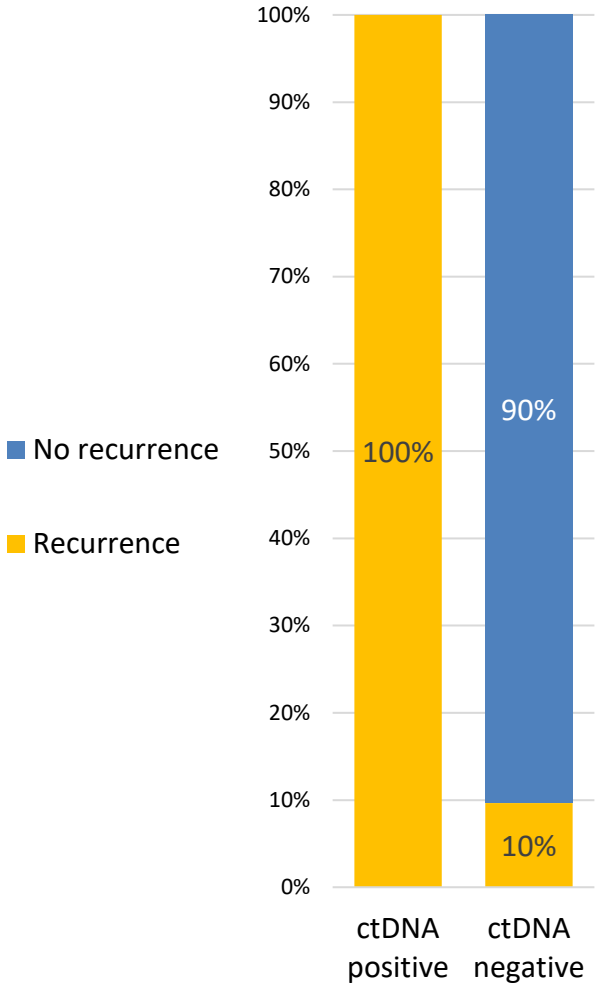
Trial Name/Country	Patient Population	Sample Size	ctDNA Assay	Timing of ctDNA Testing	Trial Intervention	Primary Objective
DYNAMIC-III (ACTRN-12617001566325) Australia/New Zealand	Stage III colon cancer	1000	Safe-SeqS	Week 5–6 post-op	**Standard of care:** clinician determined standard of care adjuvant chemotherapy based on clinical risk **ctDNA-guided:** ctDNA-positive → escalated chemotherapy regimen from pre-planned treatment (increase duration or number of agents); ctDNA-negative → de-escalated chemotherapy regimen from pre-planned treatment (reduction in duration or number of agents)	• Achieve an acceptable rate of de-escalation in the ctDNA-informed negative cohort (phase II) • Demonstrate non-inferiority of ctDNA-guided management with respect to recurrence in the de-escalation (ctDNA-informed negative) cohort (phase III) • Investigate superiority of a ctDNA-informed management with respect to recurrence in the escalation (ctDNA-informed positive) cohort (Phase III)
TRACC (NCT04050345) [79] United Kingdom	High risk stage II, stage III colorectal cancer	1621	NGS-based 22-gene colorectal panel	<8 weeks post-op, 3 months post-op	**Standard of care:** 6 months of capecitabine or 3 months of CAPOX **ctDNA-guided:** ctDNA-positive → standard adjuvant chemotherapy; ctDNA-negative → de-escalate treatment but re-escalate if ctDNA becomes positive at 3 months	• To demonstrate non-inferiority in 3-year DFS between standard of care arm and ctDNA-guided adjuvant chemotherapy arm
VEGA (UMIN000039205) [84] Japan	High-risk stage II, low-risk stage III colon cancer—ctDNA-negative	1240	Signatera™	1-month post-op	Post-op ctDNA-negative patients randomised to: **Standard of care:** 3 months of CAPOX **Experimental:** Surveillance • Patients enroll in ALTAIR study if ctDNA becomes positive at 3 months	To demonstrate the non-inferiority of observation vs. adjuvant CAPOX with absence of ctDNA at 1 month post-surgery

ctDNA has potential to be used throughout the disease course



Results during/after chemo





Shorter Recurrence-Free-Survival:
HR=51; 95%CI 15-167; P<0.001

Henriksen et, al.,
Clin Cancer Res. Oct 8, 2021

Clinical implication

Post ACT ctDNA positivity

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Microscopic residual disease

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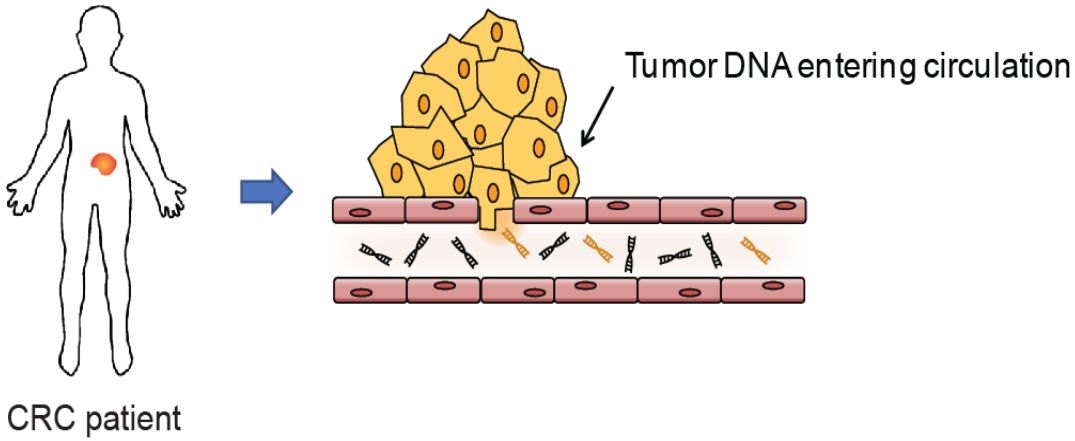
Can escalation improve survival ?



ctDNA-Enriched 2nd Line Adjuvant Therapy Trial						
ALTAIR (UMIN000039205) [85] Japan	Stage II/III colorectal cancer or stage IV with resectable metastases	240	Signatera™	1-month post-op and after 3 months of standard adjuvant CAPOX	Patients who are ctDNA-positive after completion of 3 months adjuvant CAPOX are randomised to: **Standard of care:** placebo/surveillance **Experimental:** trifluridine/tipiracil	To demonstrate the superiority of trifluridine/tipiracil over placebo in patients with ctDNA that remains positive after standard adjuvant therapy
ACT-3 (NCT04259944) United States	Stage III colorectal cancer	500	Guardant LUNAR-1™	3–6 weeks post adjuvant chemo	Patients who are ctDNA-positive after completion of 3–6 months of adjuvant FOLFOX/CAPOX are randomised to: **Standard of care:** surveillance **Experimental:** (a) FOLFIRI (MSS/BRAF wild-type) (b) Encorafenib/Binimetinib/ Cetuximab (BRAF mutant) (c) Nivolumab (MSI-H)	To demonstrate the superiority of FOLFIRI over surveillance in patients with positive ctDNA after standard adjuvant therapy

ctDNA has potential to be used throughout the patient journey