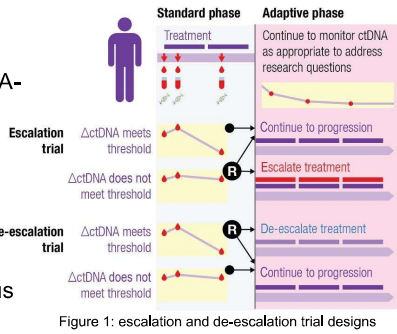


## Impact of Circulating Tumor DNA (ctDNA)-Guided Therapy on Cancer Survival

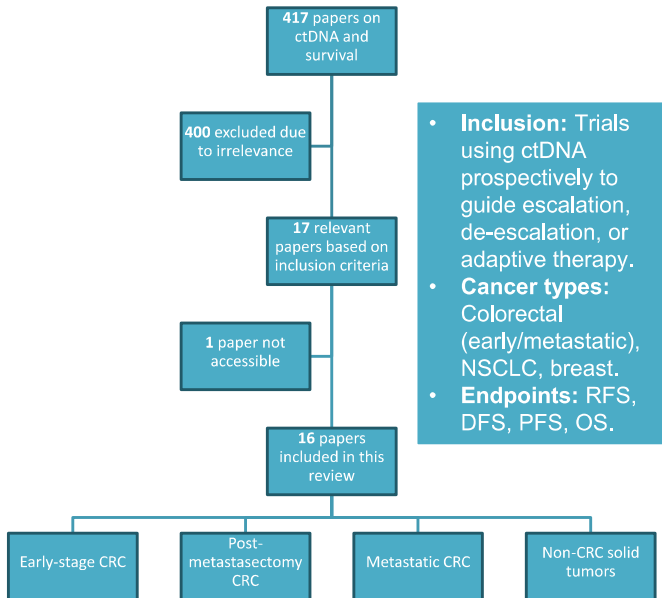
### 1 Background and Research Question

- Standard adjuvant chemotherapy (ACT) often overtreats ctDNA-negative patients
- ctDNA positivity strongly predicts recurrence across cancers
- Key question: Does acting on ctDNA status improve survival?



### 2 Objectives

- To evaluate whether ctDNA guidance affects survival outcomes (RFS, DFS, PFS, OS)
- To assess differences in outcomes by cancer type and stage (e.g., early-stage vs. metastatic)



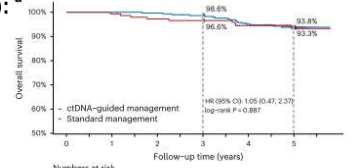
### 4 Discussion and Conclusion

- Proven:** De-escalation safe in stage II CRC (DYNAMIC); ctDNA-matched therapy improves OS in metastatic disease (GOZILA)
- Promising:** Escalation for persistent ctDNA positivity under investigation (REVISE, ALTAIR); Adaptive therapy feasible in lung and breast cancers
- Challenges:** Assay heterogeneity; Timing of sampling; Need for OS-powered RCTs
- ctDNA-guided de-escalation in early CRC preserves survival while reducing treatment
- ctDNA-based precision matching improves survival in advanced disease.
- Ongoing RCTs will determine whether escalation for MRD-positive disease improves long-term OS.

### 3 Results

#### Early-Stage Colorectal Cancer

- DYNAMIC (NEJM 2022; Nat Med 2025):**
- ACT reduced (15% vs 28%)
  - 5-yr RFS: 88% vs 87%
  - 5-yr OS: 93.8% vs 93.3%
  - ctDNA clearance → excellent survival (~97% RFS)
- TRACC, MEDOCC-CREATE, CIRCULATE:** ongoing; results pending



#### Localised Colorectal Cancer

- REVISE:** Persistent ctDNA-positive patients escalated to FOLFOXIRI vs XELOX (ongoing)
- CINTS-R:** ctDNA-guided TNT vs standard CRT in rectal cancer (ongoing)
- OPTIMISE:** Post-metastectomy stratification by ctDNA status (interim feasibility only)

#### Metastatic Colorectal Cancer

- CHRONOS (Nat Med 2022):** ctDNA-selected anti-EGFR rechallenge
- ORR 30%, DCR 63%; Improved PFS/OS compared with historical controls.
- GOZILA (Nat Med 2025):** Nationwide registry
- OS: 18.6 vs 9.9 months (HR 0.54)
  - PFS: 4.7 vs 2.8 months (HR 0.65)
  - High response in ERBB2+ and MSI-high tumours

#### Non-Colorectal Solid Tumours

##### Lung (NSCLC):

- APPLE:** Early switch to osimertinib based on ctDNA T790M → higher PFS rate, OS trend
- Dong et al., JAMA Oncol 2024:** TKI breaks in ctDNA-/CEA-negative → median PFS 18.4 mo; 96% retreatment response.
- CTONG 2201, MRD-adjuvant osimertinib:** protocols; survival outcomes pending.

##### Breast (PADA-1):

ctDNA-triggered switch from AI to fulvestrant under trial; results pending.

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