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# ctDNA Adjuvant and Oligometastasis Colon Ca
# **YES!**

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# Stage II

- Stage II – not high risk – adjuvant therapy unclear to be beneficial.

- High risk patients may benefit from adjuvant therapy
  - Lymphovascular invasion, perineural invasion, obstruction, <12 lymph nodes examined, and perforation. Close, indeterminate or positive margins

- Multi-gene assays (ColonPrint and Oncotype) may be predictive of risk of recurrence
  - However, they do not predict benefit to adjuvant chemotherapy

- ctDNA ???????-YES

J Clin Oncol. 2022;40(8):892. Epub 2021 Dec 22.

# Stage III

- Stage III Colon Cancer has lots of heterogeneity

- FOLFOX, XELOX, 5FU, Capecitabine are options

- IDEA trial 3 months =/~ 6 months of adjuvant chemotherapy
  - Except for high risk: T4 and/or N2
    - If 3 months subset analysis of IDEA collaboration suggests that CAPOX/XELOX may be a better than FOLFOX

- Still, we treat many to only benefit few
  - Analysis of 12,834 stage in IDEA, 5-year DFS from 89% T1N1a to 31% for T4N2b. The absolute DFS gain between T1N1a and T4N2b were 8% and 20%.

N Engl J Med 2004; 350:2343-2351. J Clin Oncol. 2011 Apr 10;29(11):1465-71
Lancet Oncol 2020; 21:1620. J Clin Oncol. 2022;40(8):892. Epub 2021 Dec 22.

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# ct DNA is Predictive of Recurrence Stage II Retrospective Data

- Postoperarive Colon Cancer :
  - No Adjuvant (Stage II) : ctDNA + (14 pts) and ctDNA – (164 pts):HR 18 (CI 7.9-40) independent predicting recurrence
    - **ALL 14 PATIENTS RELAPSED within 2 years**
  - Adjuvant : ctDNA + (3 pts) and ctDNA – (41 pts):HR 11 (CI 1.8-68) independent predicting recurrence
    - **ALL 3 PATIENTS RELAPSED within 10 months**

**Tie et al. Sci Transl Med, 2016**

# Is positive ctDNA sufficient to recommend adjuvant chemo in stage II? DYNAMIC

- 455 stage II 1:2 ratio
  - standard risk-factor–guided chemotherapy or
  - ctDNA positive adjuvant and ctDNA negative no.
    - The trial had a dual objective:
      - ctDNA-guided would be noninferior to standard management at 2-year RFS (primary)
      - Less chemotherapy would be used with the ctDNA-guided approach (secondary).

**J Tie et al. N Engl J Med 2022;386:2261-2272.**

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# DYNAMIC results confirmed both hypotheses:

- The 2-year recurrence-free survival was 93.5% with ctDNA-guided management and 92.4% with standard management.
- Chemotherapy use was indicated in 15% of the patients in the ctDNA-guided group and 28% of the patients in the standard-management group

**J Tie et al. N Engl J Med 2022;386:2261-2272.**

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# Is positive ctDNA sufficient to recommend adjuvant chemo in stage II?

- YES

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

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# Is negative ctDNA sufficient to not recommend adjuvant chemo in stage II?

- May be – Dynamic data support this assumption but not applicable for T4 pts

**J Tie et al. N Engl J Med 2022;386:2261-2272.**

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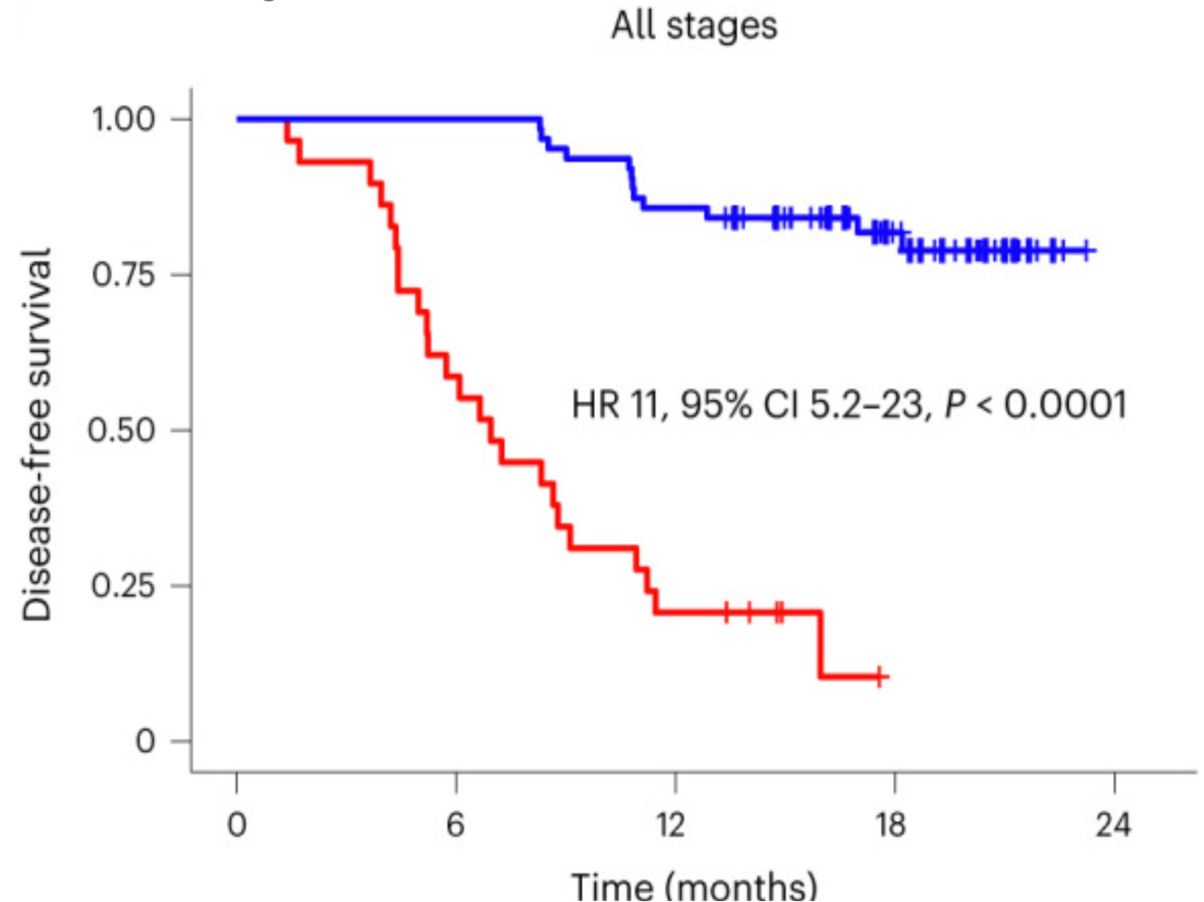
# ct DNA is Predictive of Recurrence Independent of Stage GALAXY study

- **ctDNA-+ resected stage I-IV** (tumor-informed Signatera assay) Median FU 16.7 M
  - ctDNA cleared in 68% of chemo-treated patients by 6 months after surgery
  - HR 11 (CI 5.2-23, p<0.0001) favoring clearance




Kotani D et al. Nat Med. 2023 Jan;29(1):127-134

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# Conclusions

- ctDNA MRD should be considered in colon cancer patients with stage II, III, and stage IV colon cancer post potentially curative surgery

# Many Things We Do Not Know

- What do we do when ctDNA remains or become + after adjuvant therapy
- Should we intensify adjuvant chemotherapy if ctDNA+ after 2 or 3 Months adjuvant therapy
- Should we favor tumor informed or not informed ctDNA?
- When should ctDNA be measured?
- Would ct DNA value change according to: cytotoxic X immunotherapy X targeted therapy?