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# Should we perform MRD testing in patients with resectable NSCLC in post-operative setting?

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# MRD Testing in Resectable NSCLC

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**Are we excited??**

# MRD Testing in Resectable NSCLC

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## Of course we are excited!!

- ✓ Recurrence rates following surgical resection are high (20-50%)[1].
- ✓ Current methods lack sensitivity.
- ✓ Radiographically or clinically measurable disease requires presence of millions of cancer cells[2].
- ✓ Clonal divergence and accumulation of clonal heterogeneity over time[3]
- ✓ Post-recurrence 5-yr OS remains low (˜30%)[4].

[1] Lou et al., Ann Thorac Surg 2014; [2] Fischer et al., Eur J Nucl Med Mol Imaging 2006; [3] TRACERx, Nature 2023; [4] Takenaka et al., JTCVS Open 2022

# MRD Testing in Resectable NSCLC

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## Of course we are excited!!

- ✓ Non-invasive tool!
- ✓ Elegant science!!
- ✓ Plethora of emerging data demonstrating its <u>prognostic</u> value:
  - Clearance of ctDNA -> prolonged survival[1,2]
  - Detectable ctDNA -> increased risk of recurrence and death[3,4]
  - Offers prognostic value beyond pCR in resectable NSCLC following neoadjuvant chemoimmunotherapy[5]

[1] Abbosh et al., Nature 2017; [2] Chaudhuri et al., Cancer Discov 2017; [3] Zhang et al., Cancer Discov 2022; [4] Verze et al., TLCR 2022; [5] Provencio et al., Clin Cancer Res 2026

# What major clinical decisions would you make based on the existing data?

# Let’s test this tool in the clinic!

# How does routine MRD testing help?

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- **Clinical decision making**
- **Prolong overall survival**
- **Improve quality of life**

# The Clinical Reality

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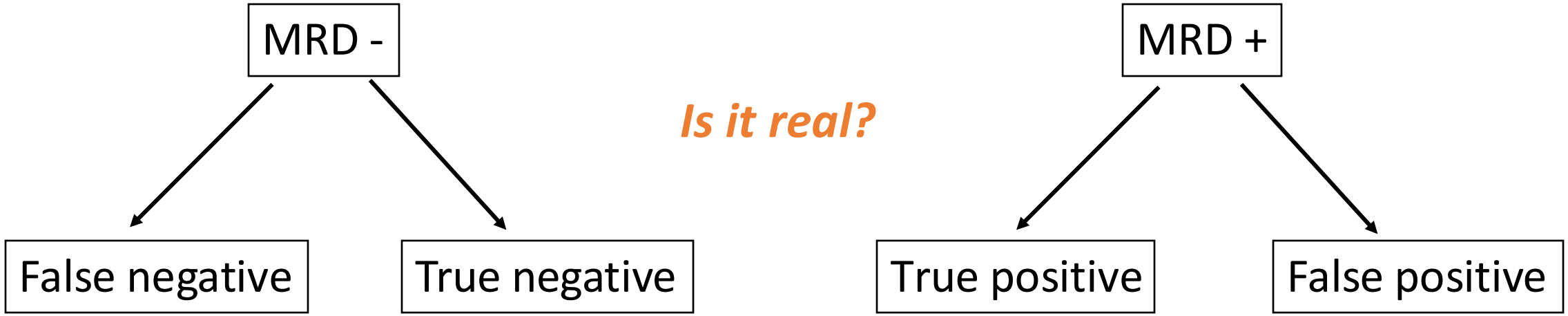


- Early-stage disease
- Low shedding tumors
- Brain-only disease
- Patients with baseline negative ctDNA
- Assay sensitivity
- Timing

False reassurance

- Is one time point enough?
- What is the optimum frequency of testing?
- Sufficient to de-escalate therapy?

- Now what?
  - More treatment?
  - Which treatment?
  - More frequent surveillance?
  - How frequent?

Psychologic cost

- CHIP mutations
- Now what?

# Impact of MRD-guided treatment approach on survival

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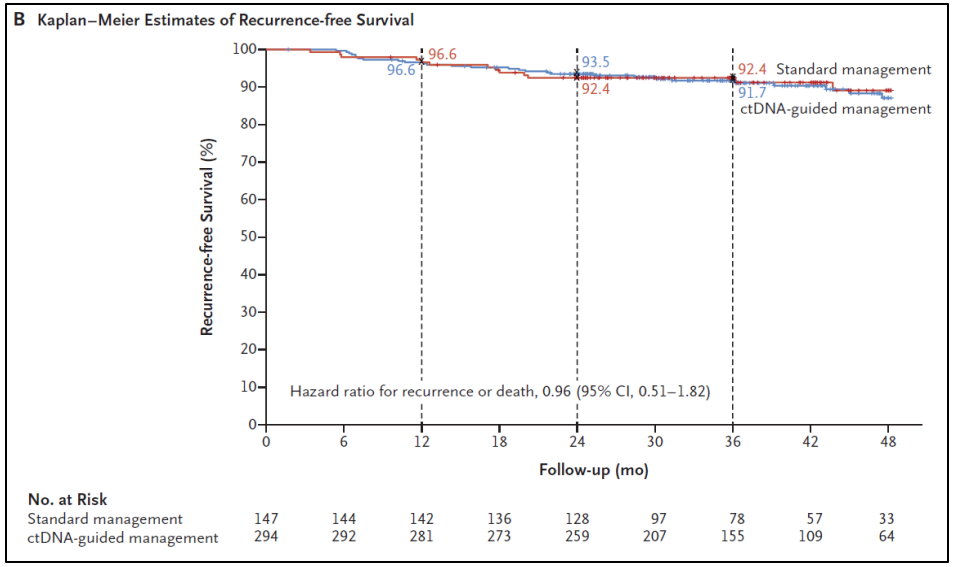
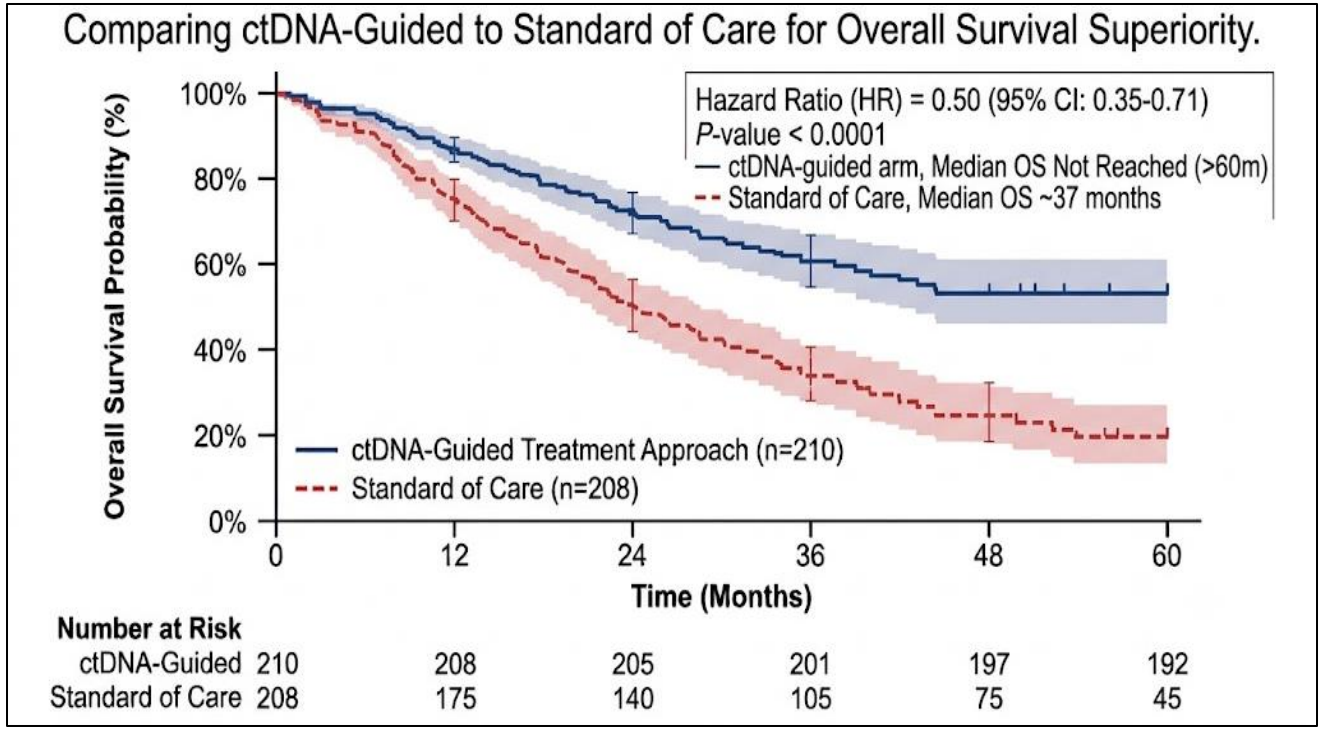
Colon Cancer




ctDNA guided adjuvant chemotherapy in <u>stage II colon cancer</u>
Tie et al., NEJM 2022 (DYNAMIC)

NSCLC




Google Gemini 2026

# How does routine MRD testing help?

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- ~~Clinical decision making~~
- ~~Prolong overall survival~~
- ~~Improve quality of life~~

# Where does MRD fit in the evidence pyramid?

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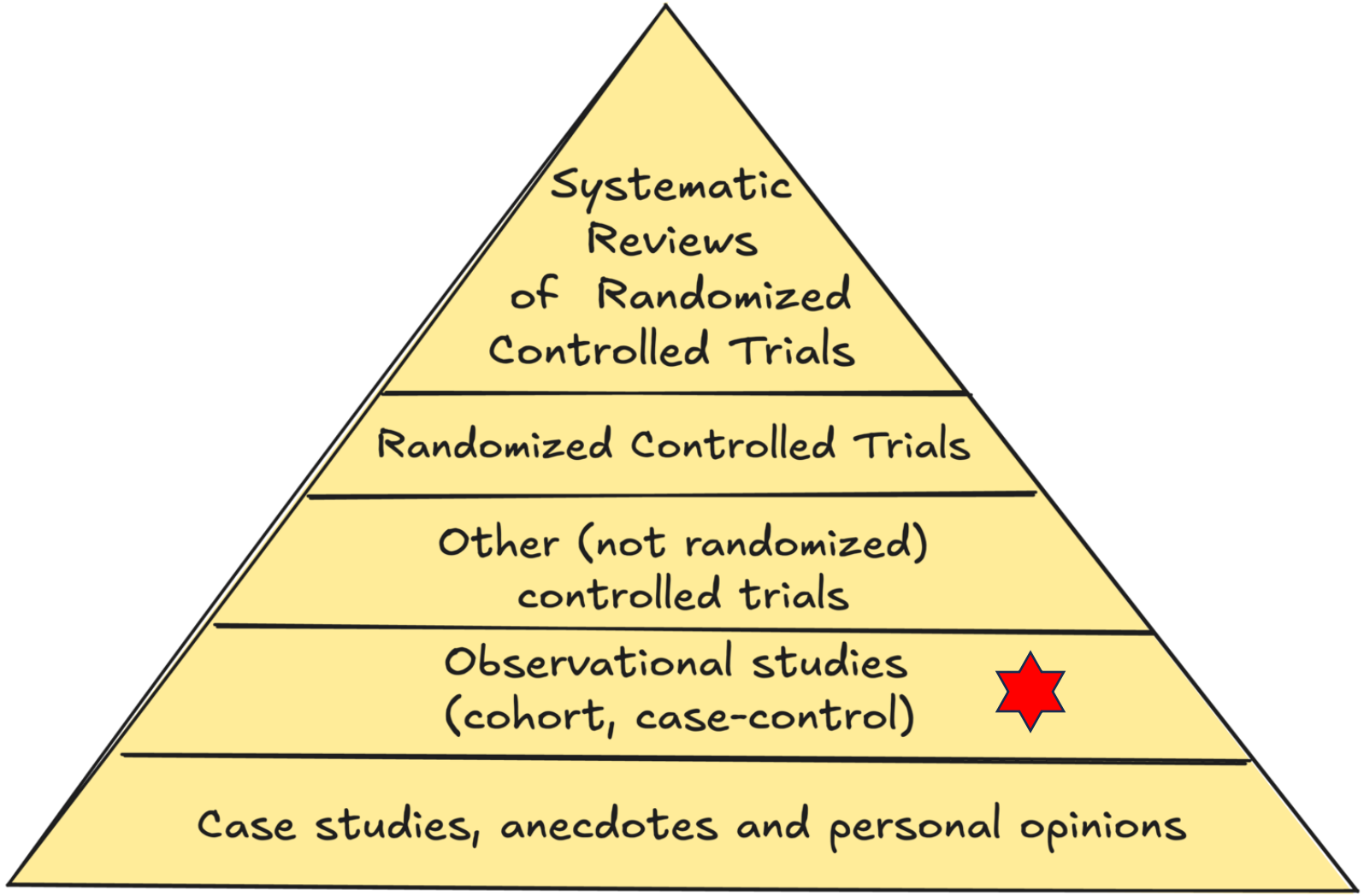

# What do we need?

- Standardized assay: sensitive, specific, cost-effective
- Optimum timing and frequency
- Define cutoff for being ‘positive’ vs ‘negative’
- Does the ‘lead time’ translate into meaningful survival benefit? If so, how much?
- **More randomized data (MRD!!)**

# Ongoing clinical trials evaluating MRD-guided adaptive management

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| Disease Stage | Phase | Measurement strategy (MRD)[#] | Molecular background | Accrual (est.) | Study arms & interventions | Primary endpoint(s) | Status | Trial Id |
|---|---|---|---|---|---|---|---|---|
| I | n/a | Landmark | ns | 342 | A (MRD+): Treatment<br>B (MRD-): Observation | 3-yr DFS | Not yet recruiting | NCT06709274 (MOTION-NSCLC) |
| IA-IIA | II | Landmark | *EGFR*-mutant | 32 | A (MRD+): Osimertinib or Observation<br>B (MRD-): Observation | PFS | Not yet recruiting | (No NCT no.) PMID: 39659920 |
| IB-IIIA | Obs. | Longitudinal | ns | 180 | (MRD-): Observation (single-arm) | 2-yr DFS | Recruiting | NCT05457049 (CTONG 2201) |
| I-III | II | Landmark | Non-mutant | 80 | A (MRD+): Durvalumab (2 C) +/− maintenance Durvalumab<br>B (MRD-): Observation | Decrease in ctDNA | Recruiting | NCT04585477 (ADAPT-E) |
| I-III | II | Landmark | ns | 66 | A (MRD+): Chemotherapy<br>B (MRD+): Observation | 2-yr RFS | Recruiting | NCT04966663 (ctDNA Lung RCT) |
| IB-IIIB | II | Longitudinal | *EGFR*-mutant | 180 | A (MRD+): Icotinib (on/off)<br>B (MRD-): Observation | 3-yr DFS | Recruiting | NCT05536505 |
| IB-IIIA | II | Landmark | Non-mutant | 80 | A (MRD+)[*]: Toripalimab<br>B (MRD-)[*]: Observation | 2-yr DFS | Recruiting | NCT06426511 (CONTINUE) |
| II-IIIA | III | Landmark | *EGFR*-mutant | 226 | A (MRD+): Osimertinib<br>B (MRD+): Observation | 3-yr DFS | Not yet recruiting | NCT06323148 (ECTOP-1022) |
| IB-IIA | Obs. | Longitudinal | ns | 150 | A (MRD+): Chemotherapy or Observation<br>B (MRD-): Chemotherapy or Observation | 3-yr DFS | Recruiting | NCT05167604 |
| III | III | Longitudinal | *EGFR*-mutant | 192 | A: Continuous Almonertinib treatment<br>B: MRD-guided Almonertinib treatment (on/off) | 18-mo EFS, 8-wk ORR | Recruiting | NCT04841811 (APPROACH) |
| III | III | Landmark | ns | 48 | A (MRD+): Chemotherapy + Durvalumab + Tremelimumab (4 C) +/− maintenance Durvalumab<br>B (MRD-): Durvalumab | Change in ctDNA after ChT | Recruiting | NCT04585490 |

Boukouris et al., Nature Precision Oncol 2025


**We should <u>NOT</u> routinely perform MRD testing in patients with resectable NSCLC in post-operative setting.**

# Guidelines say so too!

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| | |
|---|---|
| NCCN (2025) | **For NSCLC, ctDNA is not routinely recommended in early (stages I–III) settings**. For colorectal cancer, it is recognized as a prognostic marker, but there is insufficient evidence to recommend its routine use outside of clinical trials for guiding adjuvant therapy or surveillance. For Merkel cell carcinoma, it is recommended for assessing disease burden and surveillance. |
| ASCO (2022) | The lung cancer surveillance guideline **recommends against using circulating biomarkers for surveillance after curative intent therapy**, citing uncertainty as to whether the 2 to 5-mo lead time in recurrence detection translates to improved patient survival. The 2022 opinion on somatic genomic testing acknowledges the potential for ctDNA to identify patients at higher risk of recurrence but maintains **its use is investigational pending prospective validation**. |
| IASLC (2024) | Identifies MRD as a **key prognostic marker in NSCLC and suggests that MRD-positive patients may require more effective therapeutic strategies**. The papers highlight the future potential for MRD analysis to predict response to treatment and guide therapeutic intervention. |
| ESMO (2022) | Acknowledges the strong clinical validity of MRD detection for predicting relapse but notes that current assays have suboptimal sensitivity. **Due to a lack of proven clinical utility in improving patient outcomes, its use is not recommended for routine clinical practice and should be reserved for clinical trials**. |

# The Ballad of MRD

Oh, mighty MRD, with your sequencing might,
You promise to tell us what lurks out of sight.

You whisper, "Cancer!" We ask, "Now what?"
The trials reply... "Well, we've not settled that."

Sometimes you're silent when disease remains,
Sometimes you're noisy, creating new pains.

A positive test steals a patient's good sleep,
A negative one? Those promises we shouldn't keep.

So here's my advice, both humble and wise:
Before making routine what dazzles our eyes—

Let's wait for the evidence, sturdy and true...

Because just because we can measure it, doesn't mean we should do it.

*- With editorial assistance from ChatGPT*