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

Conor Steuer, MD
Associate Professor
Associate Division Director Medical Oncology
Winship Cancer Institute of Emory University

DISCLOSURES

- Advisory work for Novocure, Daiichi, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Regeneron Pharmaceuticals, Mirati, Merck, EMD Serono, AbbVie
- Thank you to Dr Mamdani for slide assistance
- I apologize as I am just learned how to use AI drawing capabilities, so bear with me

Dr Carlisle and I in 30 years, probably.



MRD Testing in Resectable NSCLC

Are we excited???

MRD Testing in Resectable NSCLC

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

Of course we are excited!!

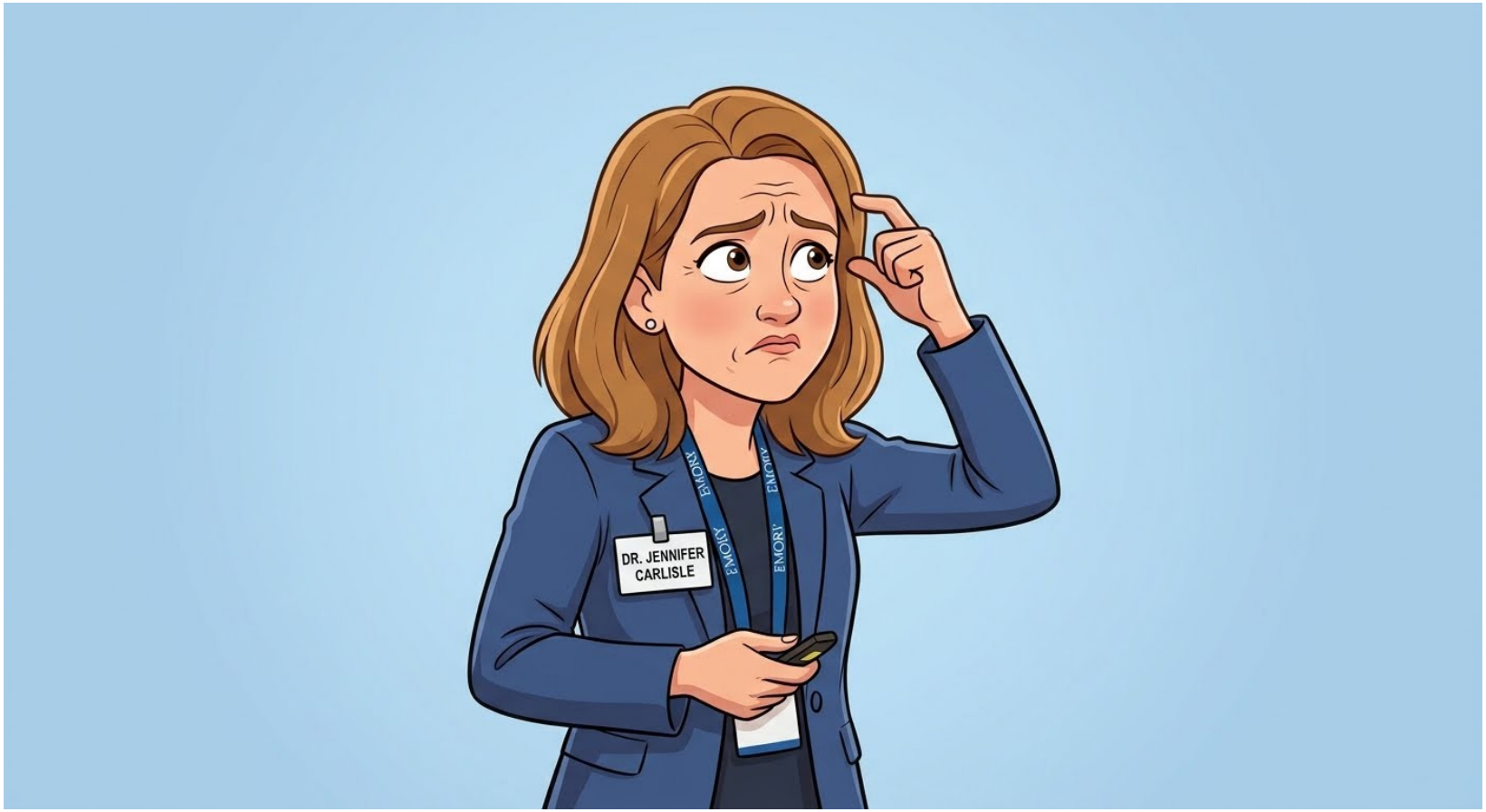




- ✓ Non-invasive tool!
- ✓ Elegant science!!
- ✓ Plethora of emerging data demonstrating its <u>prognostic</u> value:
  - Clearance of ctDNA -> prolonged survival[1,2]
  - Detectable ctDNA -> increased risk of recurrence and death[3,4]
  - Offers prognostic value beyond pCR in resectable NSCLC following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

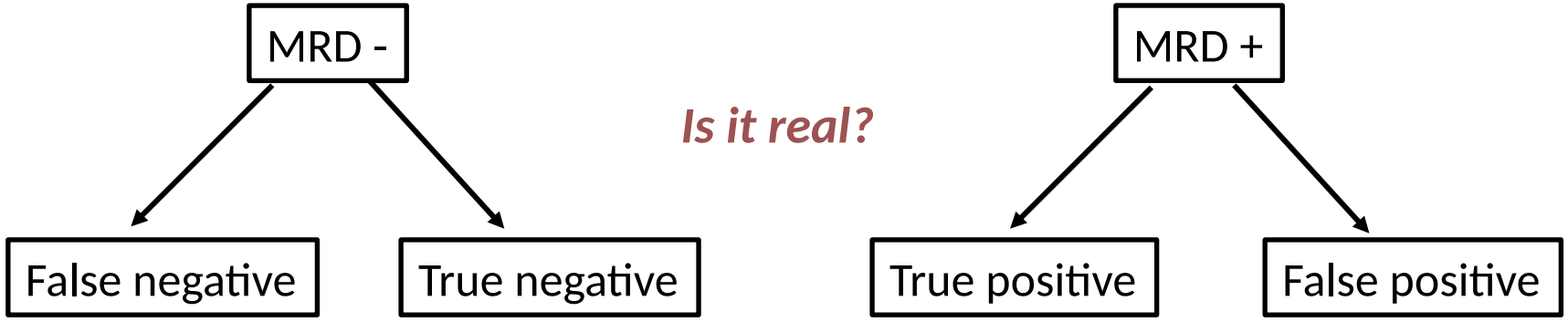
What major clinical decisions would you make based on the existing data?



How does routine MRD testing help?

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

The Clinical Reality



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

- 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?

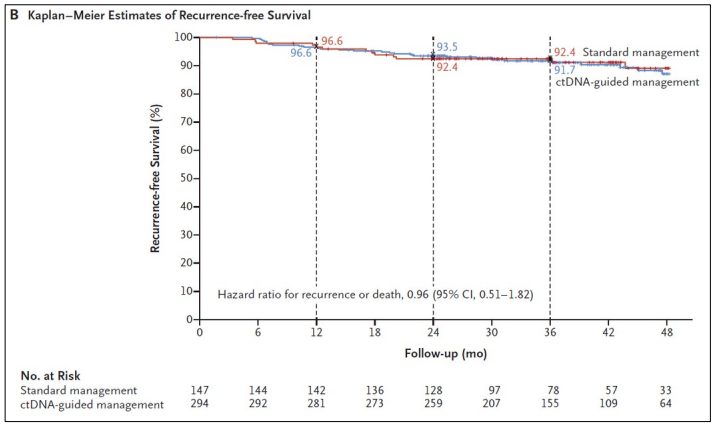
- CHIP mutations
- Now what?

False reassurance

Psychologic cost

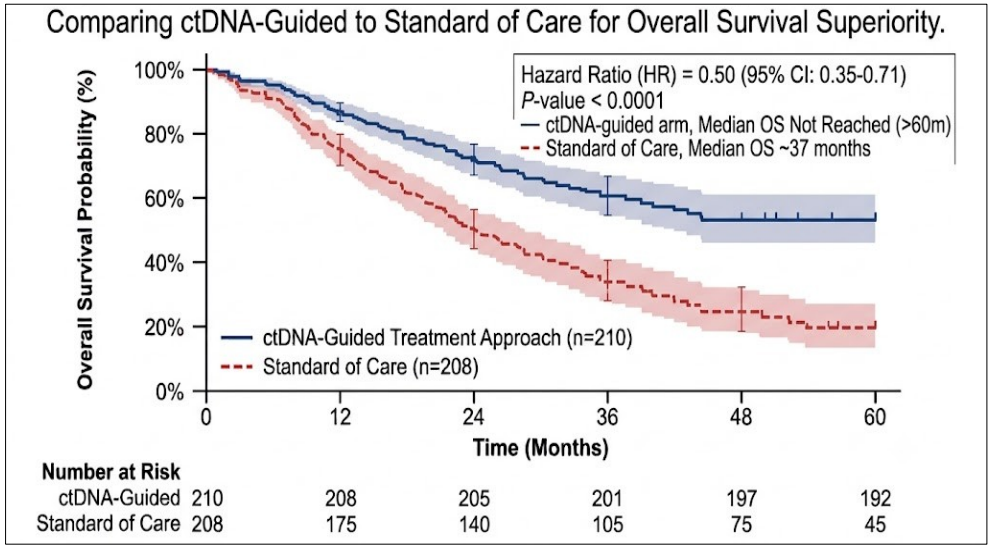
Impact of MRD-guided treatment approach on survival

Colon Cancer



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

NSCLC

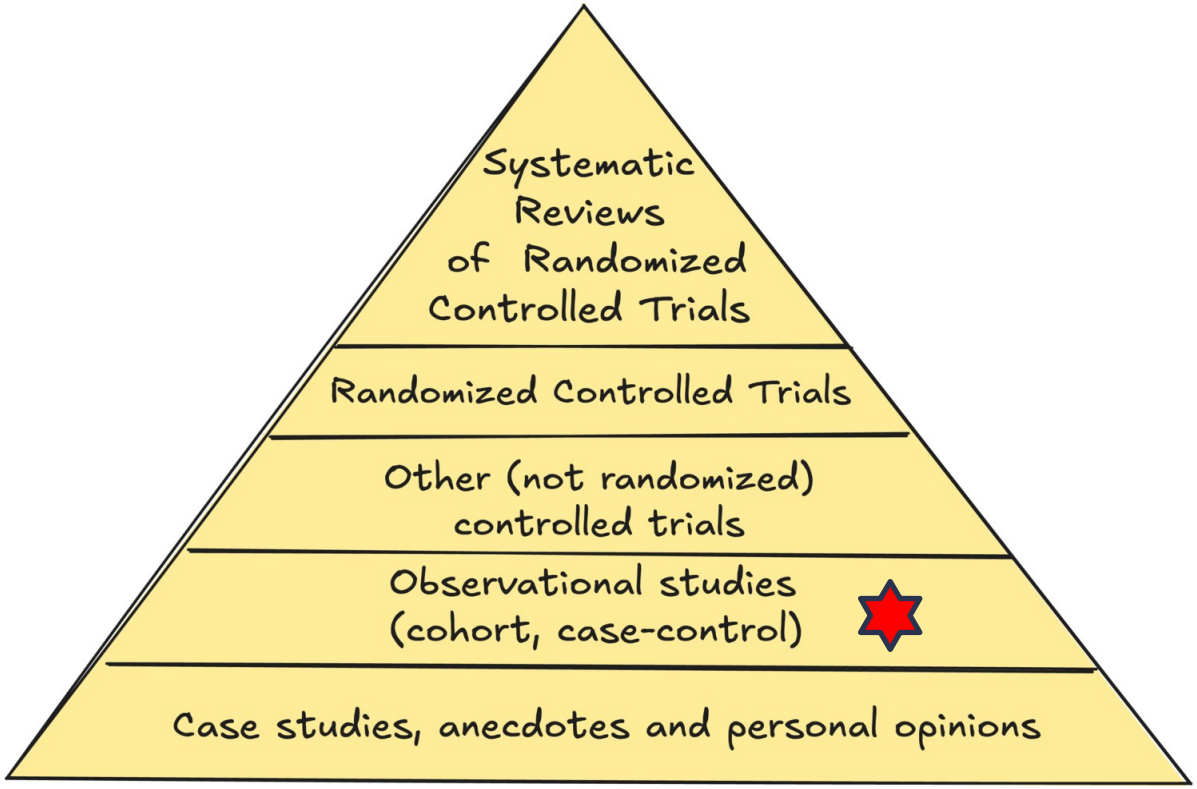


Google Gemini 2026

How does routine MRD testing help?

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

Where does MRD fit in the evidence pyramid?



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

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 B (MRD-): Observation	3-yr DFS	Not yet recruiting	NCT06709274 (MOTION-NSCLC)
IA-IIA	II	Landmark	*EGFR*-mutant	32	A (MRD+): Osimertinib or Observation 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 B (MRD-): Observation	Decrease in ctDNA	Recruiting	NCT04585477 (ADAPT-E)
I-III	II	Landmark	ns	66	A (MRD+): Chemotherapy B (MRD+): Observation	2-yr RFS	Recruiting	NCT04966663 (ctDNA Lung RCT)
IB-IIIB	II	Longitudinal	*EGFR*-mutant	180	A (MRD+): Icotinib (on/off) B (MRD-): Observation	3-yr DFS	Recruiting	NCT05536505
IB-IIIA	II	Landmark	Non-mutant	80	A (MRD+)[*]: Toripalimab B (MRD-)[*]: Observation	2-yr DFS	Recruiting	NCT06426511 (CONTINUE)
II-IIIA	III	Landmark	*EGFR*-mutant	226	A (MRD+): Osimertinib B (MRD+): Observation	3-yr DFS	Not yet recruiting	NCT06323148 (ECTOP-1022)
IB-IIA	Obs.	Longitudinal	ns	150	A (MRD+): Chemotherapy or Observation B (MRD-): Chemotherapy or Observation	3-yr DFS	Recruiting	NCT05167604
III	III	Longitudinal	*EGFR*-mutant	192	A: Continuous Almonertinib treatment 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 B (MRD-): Durvalumab	Change in ctDNA after ChT	Recruiting	NCT04585490

Boukouris et al., Nature Precision Oncol 2025

Guidelines say so too!

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.**

And of course, the ultimate voice of truth…

Hello chat gpt, should i use MRD testing in resectable NSCLC

The short answer is: **Not yet as part of routine, standard clinical care outside of a clinical trial**, but it is one of the most rapidly evolving areas in thoracic oncology.

Major clinical guidelines—such as the **National Comprehensive Cancer Network (NCCN) Guidelines**—do not currently mandate or routinely recommend making post-surgical treatment decisions (like giving or withholding chemotherapy or immunotherapy) based solely on Minimal Residual Disease (MRD) status.

The decision to use it comes down to a balance of clinical context, technological readiness, and your treatment philosophy.



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