PRECISION ONCOLOGY IN MELANOMA:

Exploring ctDNA as a Dynamic Biomarker

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DISCLOSURES

- I have no relevant financial disclosures

THE EVOLVING ROLE OF CTDNA IN MELANOMA

Why this matters:

- Melanoma remains a leading cause of cancer-related deaths, despite advances in immunotherapy and targeted therapy.
- Current methods for assessing recurrence (risk) are imprecise
- Biomarkers are essential to identify high-risk patients early and refine treatment decisions
- Integrating ctDNA can enable treatment modifications potentially optimizing patient outcomes

Key learning objectives:

- Define ctDNA and its role in Minimal Residual Disease (MRD) detection.
- Review clinical evidence supporting its predictive and prognostic value.
- Discuss applications in surveillance, treatment response, and trial design.

WHAT IS CTDNA? HOW DOES MRD TESTING WORK?

📌 **What is ctDNA?**

•Tumor-derived DNA fragments circulating in the blood.

•Released from necrotic/apoptotic cancer cells.

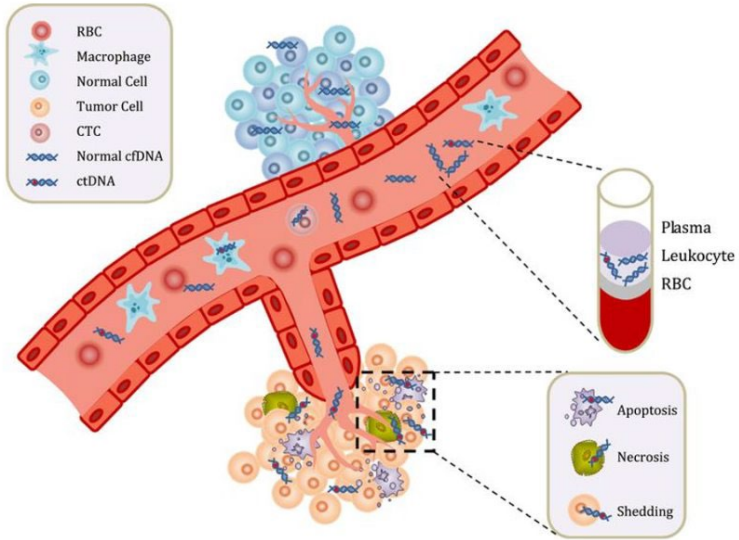
•Can be detected using **liquid biopsy** (blood draw).

📌 **What is MRD Testing?**

•**Minimal Residual Disease (MRD)** = microscopic tumor burden after treatment.

•**Goal:** Detect disease before recurrence appears clinically or on imaging.

•**Key Advantage:** Non-invasive and **more sensitive than scans**.



Hahn et al. *Kidney Cancer*. 2019;3:7–13.

TYPES OF CTDNA TESTING

Tumor informed vs Tumor agnostic

Tumor-Informed ctDNA (Personalized Panels)

•Method: Uses tumor tissue sequencing to identify patient-specific mutations, then tracks those mutations in plasma.

✅ Advantages:

Higher sensitivity and specificity for detecting MRD.

Personalized approach minimizes false positives.

❌ Disadvantages:

- Requires initial tumor biopsy for sequencing.
- Not useful for patients without an available or sufficient tumor sample.
- May miss tumor evolution if new mutations emerge.

Tumor-Agnostic ctDNA (Fixed Panels or Epigenetic Markers)

•Method: Uses predefined mutation panels, methylation markers, or fragmentomics to detect ctDNA without prior tumor sequencing.

✅ Advantages:

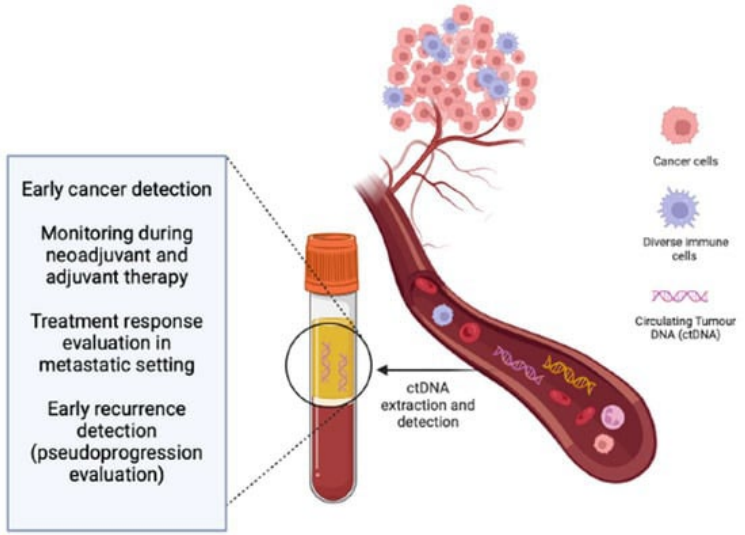
- No need for tumor tissue, making it broadly applicable.
- Can detect tumor evolution and new resistance mutations.
- Easier to implement in clinical settings.

❌ Disadvantages:

- Lower specificity—may detect mutations from clonal hematopoiesis or non-relevant alterations.
- Less sensitive for MRD detection compared to tumor-informed approaches.

WHY MELANOMA IS IDEAL FOR CTDNA MONITORING

- High Mutational Burden
- Early Bloodstream Spread
- Heterogeneous Disease Biology
- Clinicopathologic factors (e.g., stage, LDH levels) lack precision in recurrence risk
- Lead Time Advantage for Immunotherapy



CTDNA AS PROGNOSTIC MARKER

Can ctDNA predict PFS and OS in melanoma?

- **High-risk stage II/III melanoma**
- **Detectable ctDNA had significantly increased risk of recurrence compared with those with undetectable ctDNA**

ESMO

Annals of Oncology 29: 490–496, 2018
doi:10.1093/annonc/mdx717
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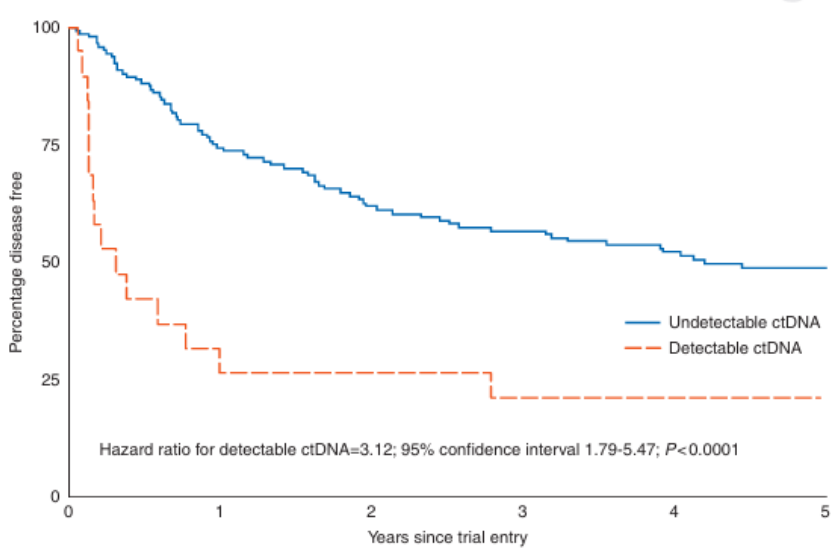
ORIGINAL ARTICLE

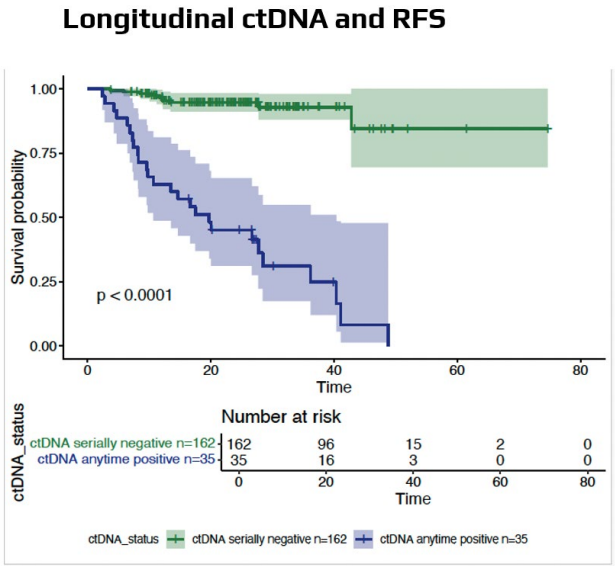
Circulating tumor DNA predicts survival in patients with resected high-risk stage II/III melanoma

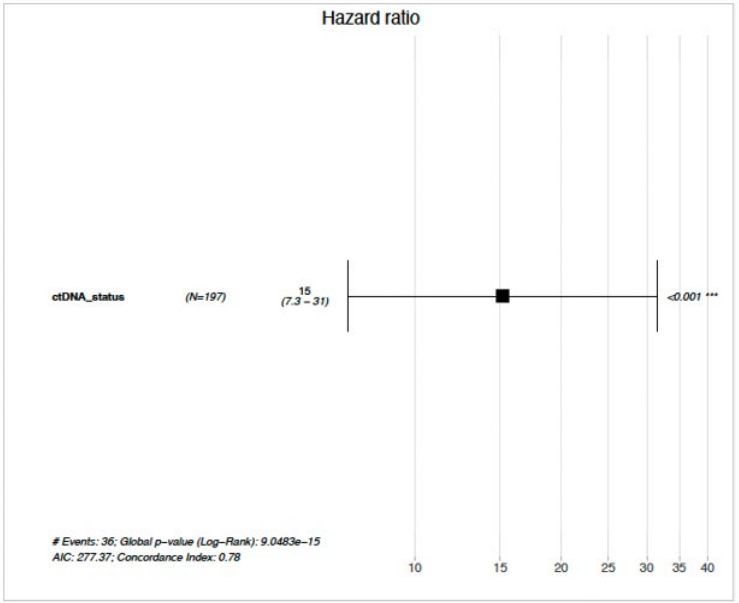
R. J. Lee[1†], G. Gremel[1†], A. Marshall[2], K. A. Myers[3], N. Fisher[3], J. A. Dunn[2], N. Dhomen[1], P. G. Corrie[4], M. R. Middleton[3], P. Lorigan[5,6] & R. Marais[1*]



CTDNA AS PROGNOSTIC MARKER

ASCO 2025 Abstract

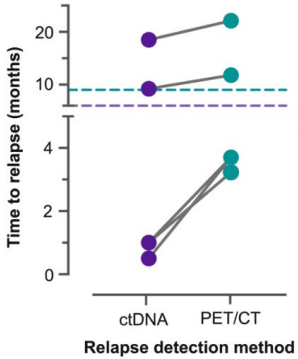


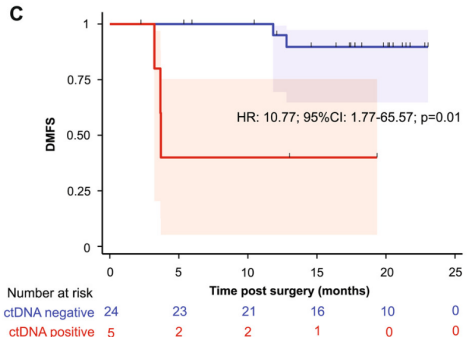


CTDNA FOR DETECTING RELAPSE

Can ctDNA detect melanoma relapse?

- This study evaluated a personalized, tumor-informed ctDNA assay in 69 patients with advanced melanoma
- Cohort A with stage III melanoma in adjuvant setting
  - Sensitivity: 83% for detecting distant melanoma relapse.
  - Specificity: 96%, meaning ctDNA-negative patients had a low likelihood of recurrence.
  - Lead time of 3 months over standard imaging





CTDNA FOR RESPONSE MONITORING

Can ctDNA be used to predict response to immunotherapy?

- **Early Detection of Non-Responders: Increasing ctDNA levels within 6 weeks of immune checkpoint inhibitor (ICI) therapy predicts poor response and shorter PFS.ctDNA Clearance Indicates Benefit:**
- **Patients who clear ctDNA during treatment have better long-term outcomes and higher response rates to ICIs.**
- **Real-Time Monitoring Advantage: ctDNA provides a faster and more dynamic assessment of response compared to traditional imaging, detecting progression months earlier.**

CONCLUSION

Key Takeaways

- How ctDNA can enhance precision medicine in melanoma
- Q&A session