Controversies in Breast Cancer: Use of ctDNA to Tailor Systemic Adjuvant / Post-neoadjuvant Therapies

CON - Mark Pegram, MD **vs** PRO - Joyce O'Shaughnessy, MD

REVIEW ARTICLE
https://doi.org/10.1038/s43018-020-0043-5
nature cancer
Check for updates

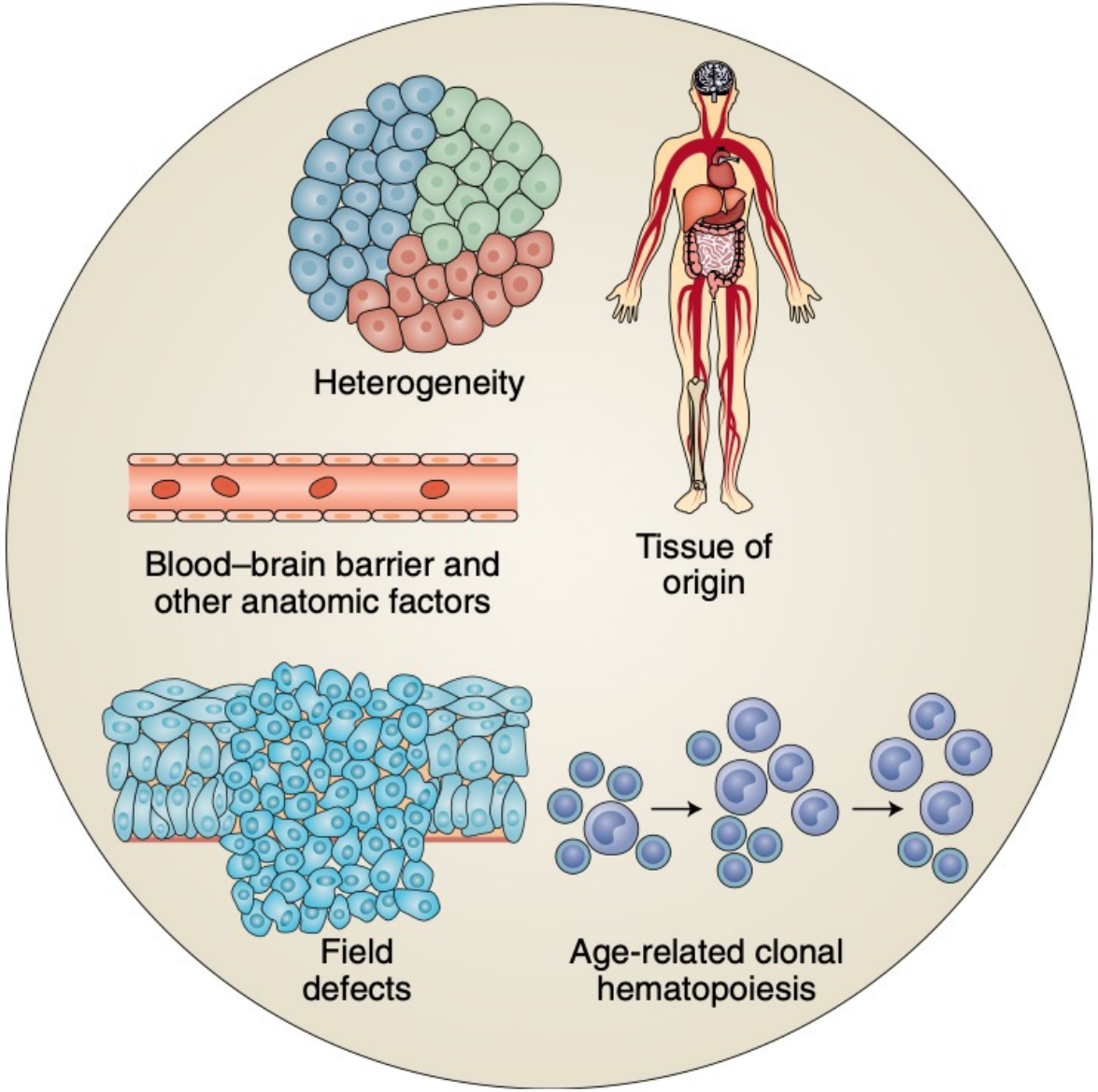
Circulating tumor DNA and liquid biopsy in oncology

David W. Cescon[1], Scott V. Bratman[2], Steven M. Chan[1] and Lillian L. Siu[1]✉

"…studies so far have shown that plasma-based testing generally fails to detect ~20% of alterations present in the tumor and identifies additional alterations of interest in a minority of cases"[1-3].

1. Li, B. T. et al. Ultra-deep next-generation sequencing of plasma cell-free DNA in patients with advanced lung cancers: results from the Actionable Genome Consortium. *Ann. Oncol.* **30**, 597–603 (2019).
2. Aggarwal, C. et al. Clinical implications of plasma-based genotyping with the delivery of personalized therapy in metastatic non-small cell lung cancer. *JAMA Oncol.* **5**, 173–180 (2019).
3. Clark, T. A. et al. Analytical validation of a hybrid capture-based next-generation sequencing clinical assay for genomic profiling of cell-free circulating tumor DNA. *J. Mol. Diagn.* **20**, 686–702 (2018).

Potential issues and drawbacks for ctDNA-based testing



- "The ideal [time] window for detecting MRD is uncertain"
  Abbosh, C., Birkbak, N. J. & Swanton, C. …challenges to implementing ctDNA-based screening and MRD detection. Nat. Rev. Clin. Oncol. 15, 577–586 (2018).

- "Case studies showed a wide range of costs,…[up] to $9124 per sample…"
  Kramer A, et al. J Mol Diagn. 2023 Jan; 25(1):36-45.

Cescon DW, Bratman SV, Chan SM, Siu LL. Circulating tumor DNA and liquid biopsy in oncology. Nat Cancer. 2020 Mar;1(3):276-290.

Simultaneously assessed exome profiles of tumor and ctDNA have…been compared (in patients with breast cancer…)

- "[Only] 88% of clonal single- nucleotide variants (SNVs) and 47% of subclonal SNVs detected in tissue were identifiable in cfDNA".

- "Conversely, 12% of clonal SNVs and 55% of subclonal SNVs in ctDNA were not detected in the tumor".

  - **The implications of these alterations detected exclusively in ctDNA and absent from simultaneously acquired tissue biopsies (i.e. whether they improve or worsen the predictive value of a given genomic biomarker) remain open questions for investigation…**

Adalsteinsson, V. A. et al. Scalable whole-exome sequencing of cell-free DNA reveals high concordance with metastatic tumors. *Nat. Commun.* **8**, 1324 (2017).

The variant allele frequency (VAF) of mutant clones is an important consideration if ctDNA is to be used as a measure of MRD

- a spherical nodule with a diameter of 4 mm would be equal to a plasma VAF of 0.00018% (95% confidence interval, 0.0000098–0.0033%).
- Such low frequencies are often below the limits of detection of current ctDNA platforms, and these thresholds are further challenged by the diminished volume of residual disease in the MRD setting.
- For a single alteration, a low VAF may fall below the physical limits of ctDNA detection with an acceptable blood volume.

Abbosh, C. et al. *Nature* **545**, 446–451 (2017).

Clinical Feasibility of serial ctDNA Analysis Has Been Called Into Question

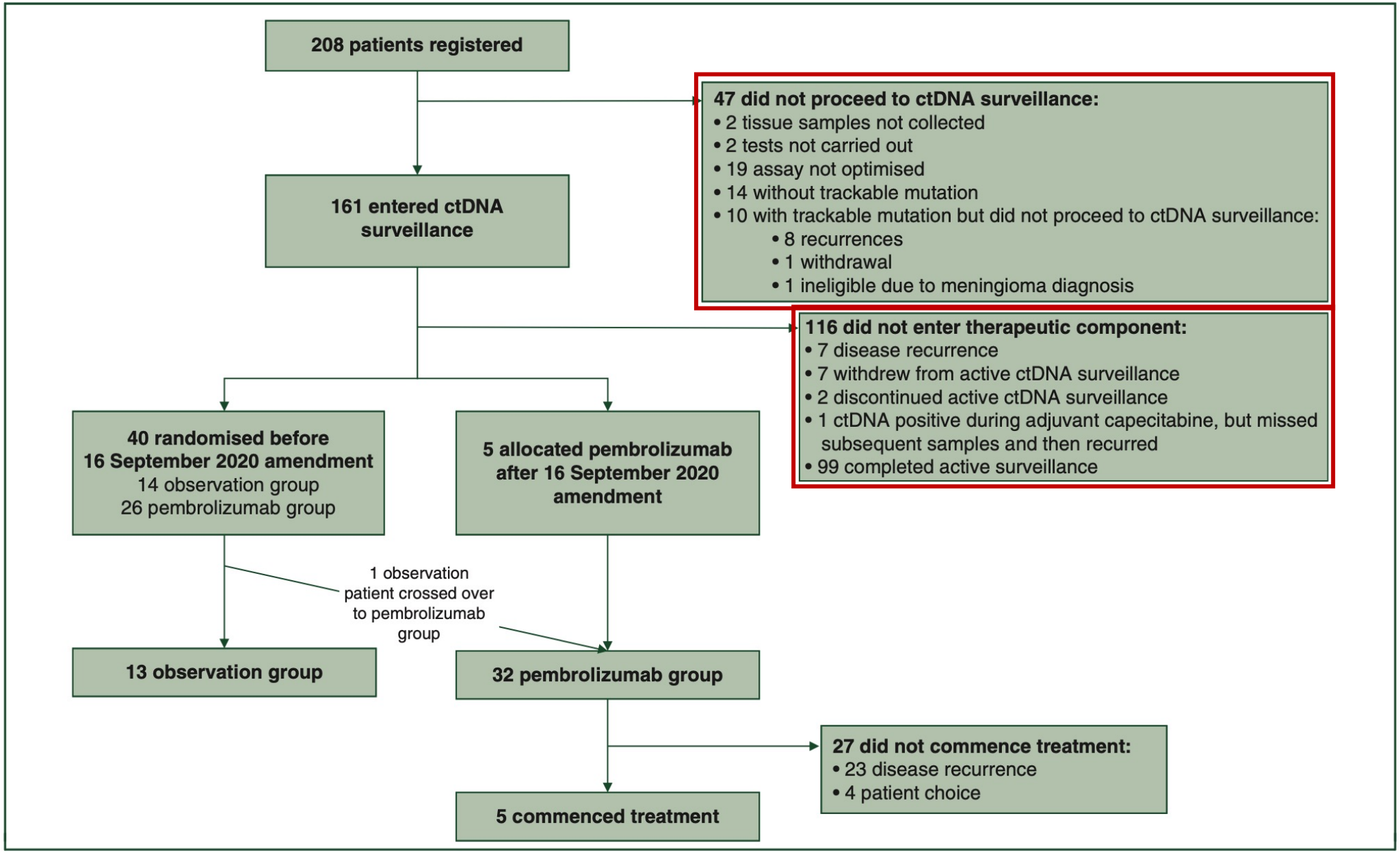
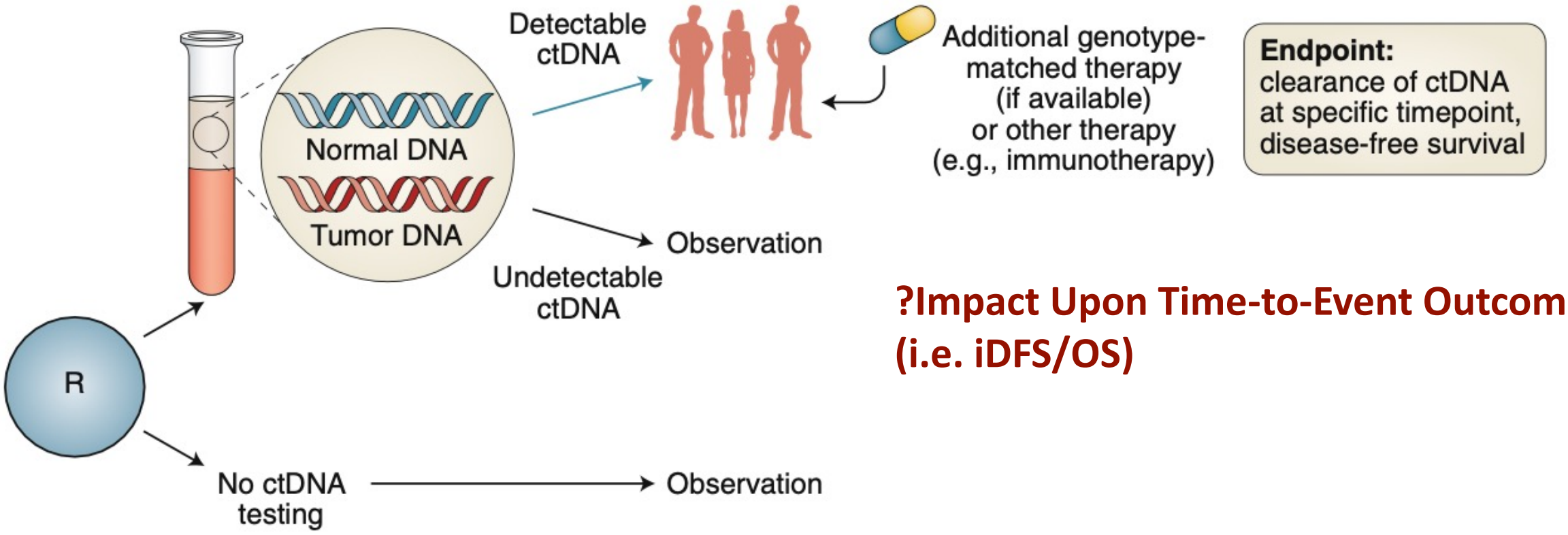


Figure 2. Consort diagram of c-TRAK TN study.
ctDNA, circulating tumour DNA.

Turner NC, et al. Ann Oncol. 2023 Feb;34(2):200-211.

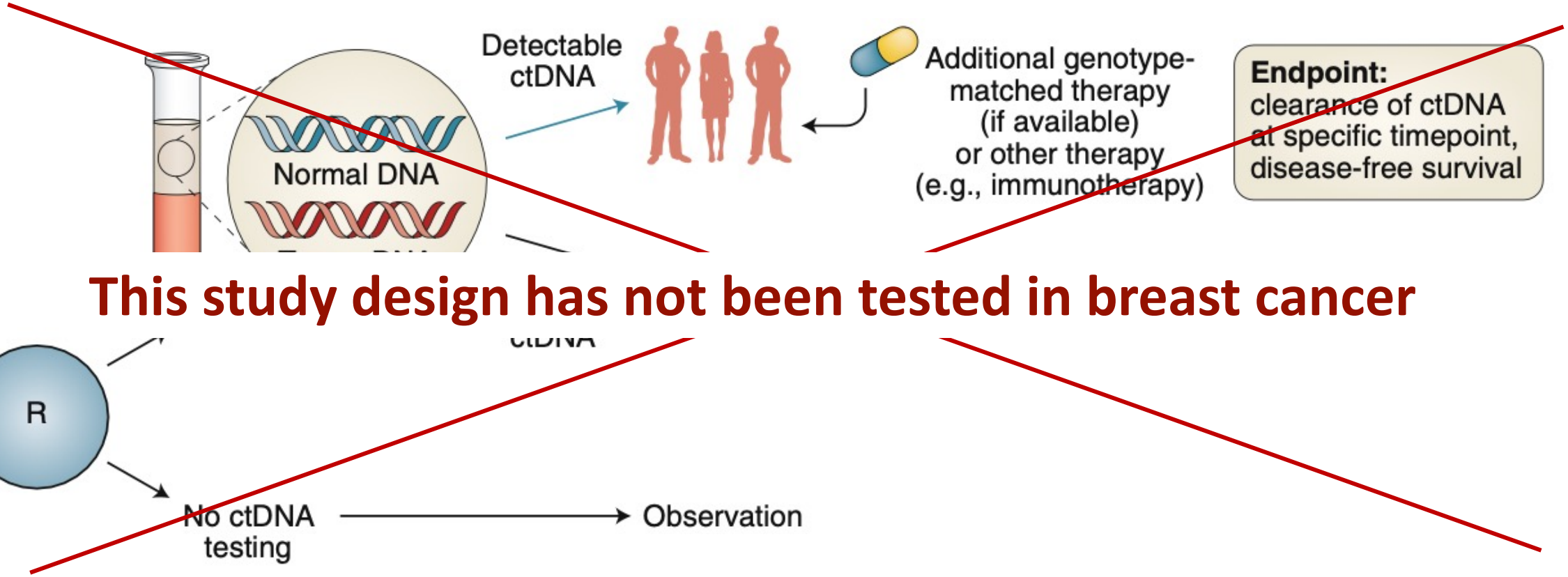
Gold Standard Prospective Biomarker Validation Study Design



?Impact Upon Time-to-Event Outcomes (i.e. iDFS/OS)

Cescon DW, Bratman SV, Chan SM, Siu LL. Circulating tumor DNA and liquid biopsy in oncology. Nat Cancer. 2020 Mar;1(3):276-290.

Gold Standard Prospective Biomarker Validation Study Design



This study design has not been tested in breast cancer

Cescon DW, Bratman SV, Chan SM, Siu LL. Circulating tumor DNA and liquid biopsy in oncology. Nat Cancer. 2020 Mar;1(3):276-290.

ctDNA Dynamics Over Time

Annals of Oncology

N. C. Turner et al.

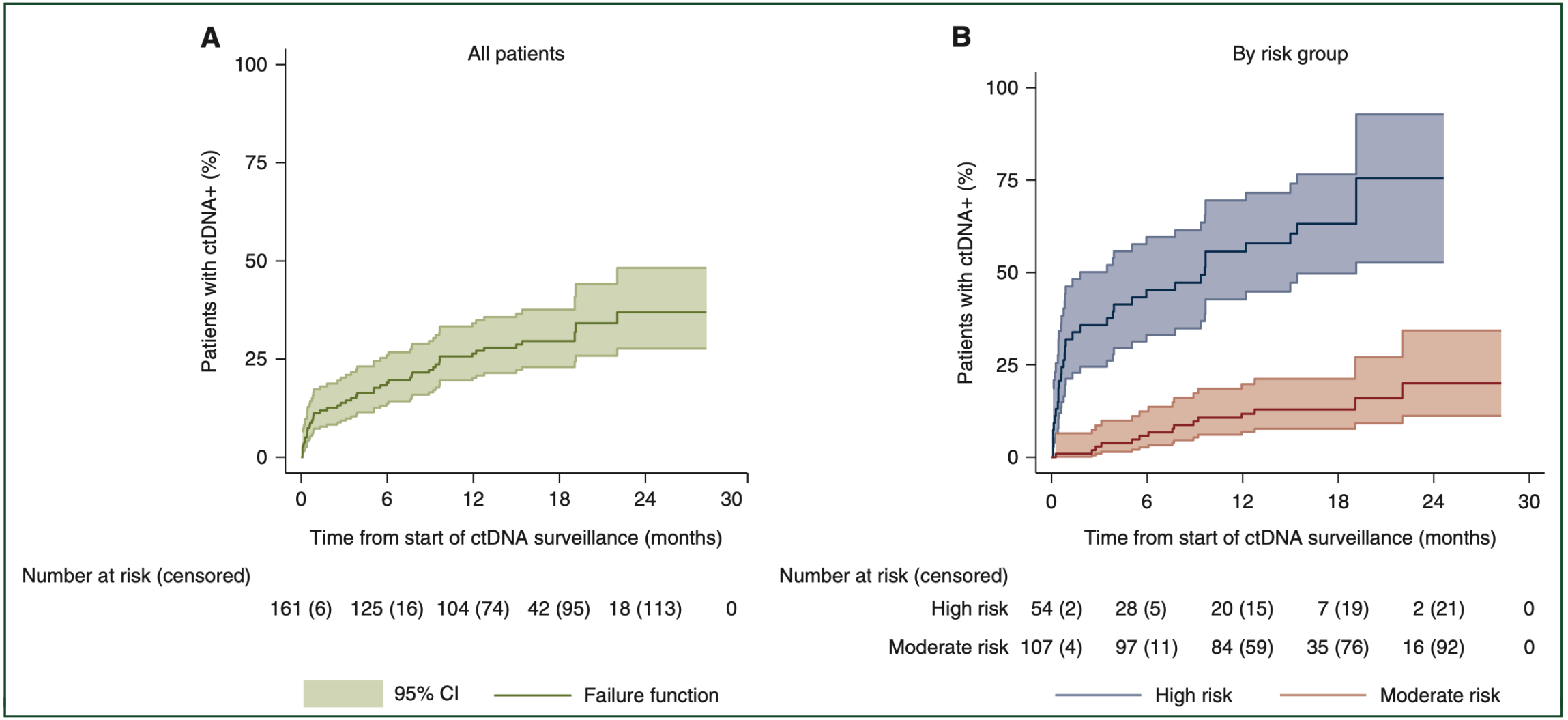
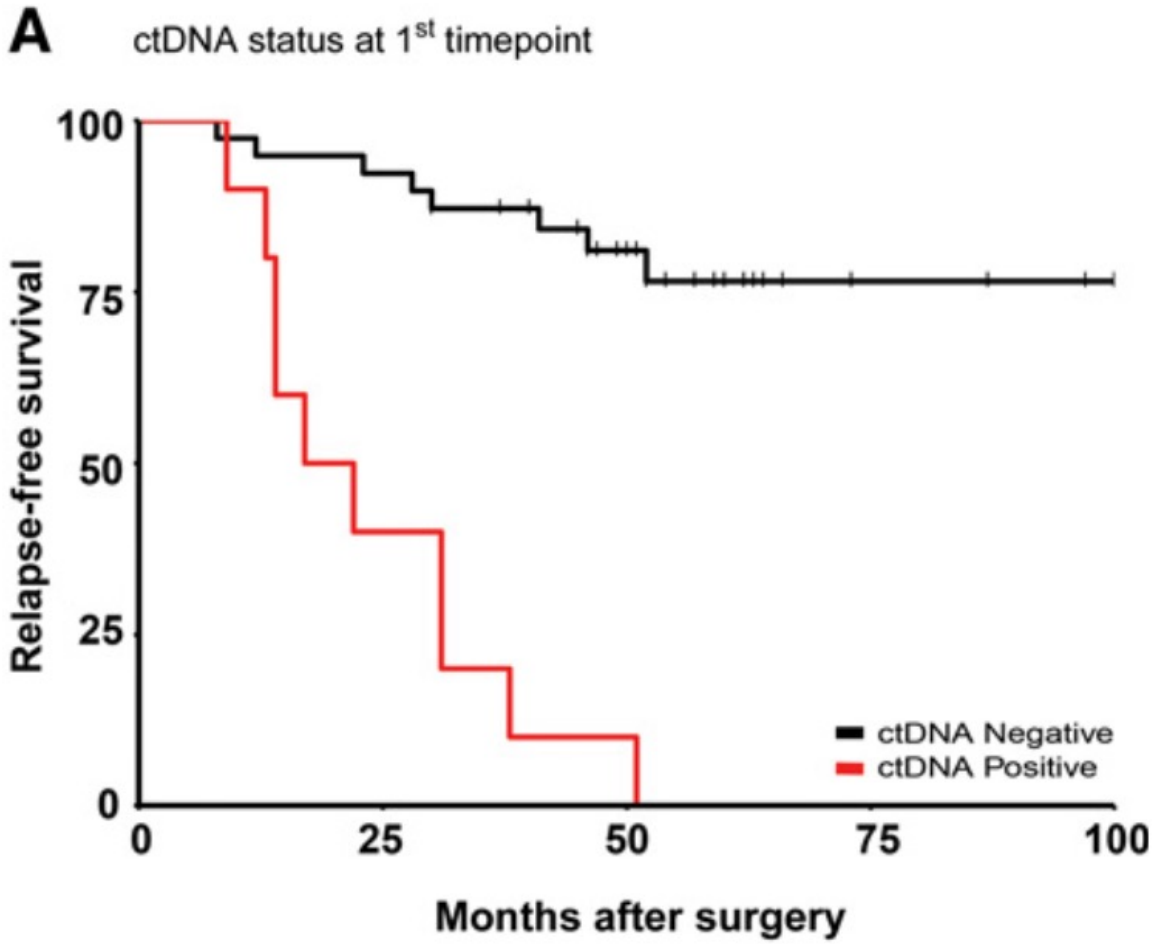


Figure 3. ctDNA detection over time. (A) Rates of ctDNA detection in the whole study population, months from the start of ctDNA surveillance. (B) Rates of ctDNA detection in moderate- and high-risk patients, months from the start of ctDNA surveillance.
CI, confidence interval; ctDNA, circulating tumour DNA.

Turner NC, et al. Ann Oncol. 2023 Feb;34(2):200-211.

1. Negative ctDNA result could yield a false sense of security



Coombes RC, et al. Clin Cancer Res. 2019 Jul 15;25(14):4255-4263.

2. "Understandably, detection of MRD without radiologic correlation is a cause for patient and provider anxiety"!

Relton A, Collins A, Guttery DS, et al: Patient acceptability of circulating tumour DNA testing…. *Eur J Cancer Care (Engl)* 30:e13429, 2021

No Guideline Recommendations for ctDNA Use in Breast Cancer

NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 5.2023 — December 5, 2023

NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients

Continue

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2023
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SURVEILLANCE/FOLLOW-UP

Exam:
- History and physical exam 1–4 times per year as clinically appropriate for 5 y, then annually

Genetic screening:
- Periodic screening for changes in family history and genetic testing indications and referral to genetic counseling as indicated, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

Post surgical management:
- Educate, monitor, and refer for lymphedema management, see NCCN Guidelines for Survivorship: Lymphedema.

Imaging:
- Mammography every 12 mo[ddd]
- Routine imaging of reconstructed breast is not indicated
- For patients with germline mutations or family history of breast cancer, please refer to See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic
- For patients receiving anthracycline-based therapy, see NCCN Guidelines for Survivorship for echocardiogram recommendations.

Screening for metastases:
- In the absence of clinical signs and symptoms suggestive of recurrent disease, there is no indication for laboratory or imaging studies for metastases screening.

Post treatment monitoring:
- Cardiotoxicity monitoring for patients who received left-sided radiation therapy, anthracyclines, or HER2-targeted therapy. For anthracycline-induced toxicity, See NCCN Guidelines for Survivorship
- Provide guidance on risk of comorbidities

Endocrine therapy:
- Assess and encourage adherence to adjuvant endocrine therapy
- Patients on tamoxifen:
  - Age-appropriate gynecologic screening
  - Routine annual pelvic ultrasound is not recommended
- Patients on an aromatase inhibitor or who experience ovarian failure secondary to treatment should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter[eee]

Lifestyle:
- Evidence suggests that active lifestyle, healthy diet, limited alcohol intake, and achieving and maintaining an ideal body weight (20–25 BMI) may lead to optimal breast cancer outcomes

Communication:
- Coordination of care between the primary care provider and specialists is encouraged. Additionally, a personalized survivorship treatment plan including personalized treatment summary of possible long-term toxicity and clear follow-up recommendations is recommended. See NCCN Guidelines for Survivorship

Engagement:
- Patients frequently require follow-up encouragement in order to improve adherence to ongoing screening and medication adherence

See Recurrent Disease (BINV-18)

CONCLUSION -- There *is* no controversy

Controversies in Breast Cancer: Use of ctDNA to Tailor Systemic Adjuvant / Post-neoadjuvant Therapies

CON - Mark Pegram, MD **vs** PRO - Joyce O'Shaughnessy, MD

In January 2024, use of ctDNA cannot be justified to tailor (neo)/adjuvant/post-neoadjuvant systemic therapies in non-metastatic breast cancer for the following 10 reasons:

1. **Lack of adequate sensitivity in the available commercial assays [Cescon, et al Nature Cancer (2020], especially when low VAF**
2. **Differing rates of release of ctDNA from different tumor/anatomical sites (e.g. BBB)**
3. **False positive results from pre-malignant field defects and clonal hematopoiesis**
4. **High cost, and unnecessary repeat imaging studies $$ [Kramer, et al. J Mol Diagn 2023]**
5. **Uninspiring clinical feasibility in recent studies [Turner, et al Ann Oncol (2023)]**
6. **Prospective phase III validation comparing ctDNA-*tested* versus *untested* on long-term time-to-event outcomes (iDFS/OS) is lacking**
7. **Negative ctDNA result could yield a false sense of security [Coombes, et al. Clin Cancer Res. 2019]**
8. **Time point(s) to acquire ctDNA are not well established – may require series testing [Turner NC, et al. Ann Oncol]**
9. **MRD without radiologic correlation is a cause for undue patient and provider anxiety [Relton, et al *Eur J Cancer Care (Engl)* 30:e13429, 2021]**
10. **August guidelines committees do not recommend ctDNA testing in the clinical management of breast cancer [NCCN, v.5 2023]**