2025 DEBATES AND DIDACTICS in Hematology and Oncology

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center
Where Science Becomes Hope

JULY 24 - 27, 2025 • SEA ISLAND, GEORGIA

This activity is jointly provided by Partners for Advancing Clinical Education and Bio Ascend

Is There a Role for Checking ctDNA in Early-Stage Breast Cancer?

YES

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Disclosures

Consultant/Advisor/Speaker: Astrazeneca, Daiichi Sankyo, Eli Lilly, Gilead

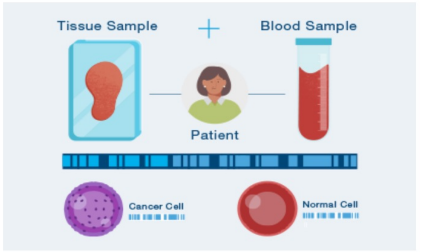
Eyes Wide Open: Current State in EBC

- Physical examination and imaging remain standard method to monitor for relapse, as well as stage disease[1]
  - Do not recommend routine labs or tumor markers to monitor for relapse
- Validation of ctDNA as a dynamic, prognostic marker in EBC
- Growing knowledge on the therapeutic and/or survival impact of early detection of molecular recurrence

IT'S HERE

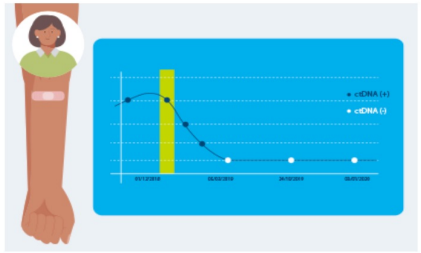
Monitor Your Breast Cancer

The Signatera™ Residual Disease Test is a custom-built blood test for people who have been diagnosed with breast cancer or other solid tumors. Signatera™ can detect molecular residual disease (MRD) in the form of circulating tumor DNA—small fragments of DNA released by cancer cells.



The first time your doctor orders Signatera™, a one time tissue sample and a blood sample are needed to build your unique test. Natera will work with your cancer care team to access your tumor tissue from a prior procedure or surgery.

After your test is built, you will need to get your blood drawn each time your doctor orders Signatera™.

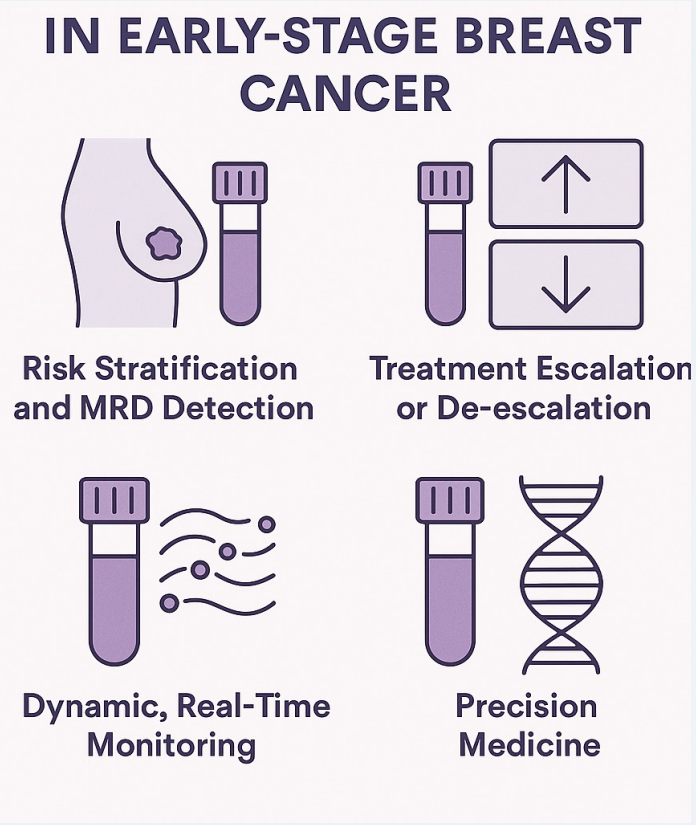


Repeated Signatera™ testing can show changes in your ctDNA levels, helping your doctor understand if your cancer is shrinking, growing, or coming back.

Clinicians should enter ordering with their eyes wide open to the strengths, inherent implications, and limitations.

1. Vaz SC, et al. Joint EANM-SNMMI guideline on the role of 2-[^{18}F]FDG PET/CT in no special type breast cancer : (endorsed by the ACR, ESSO, ESTRO, EUSOBI/ESR, and EUSOMA). Eur J Nucl Med Mol Imaging. 2024 Jul;51(9):2706-2732.
2. Cohen SA, Liu MC, Aleshin A. Practical recommendations for using ctDNA in clinical decision making. Nature. 2023 Jul;619(7969):259-268. doi: 10.1038/s41586-023-06225-y. Epub 2023 Jul 12. PMID: 37438589.
3. Yu L, et al. PLoS One. 2022 Apr 28;17(4):e0266889.

OVERVIEW – SUPPORT of ctDNA in EBC (PROGNOSTIC VALUE)



1. Risk Stratification and Minimal Residual Disease (MRD) Detection
ctDNA allows noninvasive detection of MRD post-surgery and/or (neo)adjuvant therapy.

-**c-TRAK-TN trial** (TNBC) - early-stage TNBC patients with detectable ctDNA post-treatment had significantly higher relapse risk
  -Rate of ctDNA detection by 12 months was 27.3%
  ->70% had metastases on imaging at time of +ctDNA

-**ZEST trial** (TNBC and BRCAm HER2-) - early-stage breast cancer patients with ctDNA positivity after therapy had a >60% risk of recurrence within 2 years, versus <15% in ctDNA-negative patients.
  -Closed early due to low rates of +ctDNA and ~50% having metastatic disease at time of +ctDNA

2. Dynamic, Real-Time Monitoring
Unlike static clinicopathologic markers (e.g., tumor size, nodal status), ctDNA provides **real-time, personalized tumor monitoring for** relapse/progression or clearance post-treatment.

-Several tumor-informed ctDNA platforms demonstrate analytical and clinical validity w/ ~8 -10 mos lead time

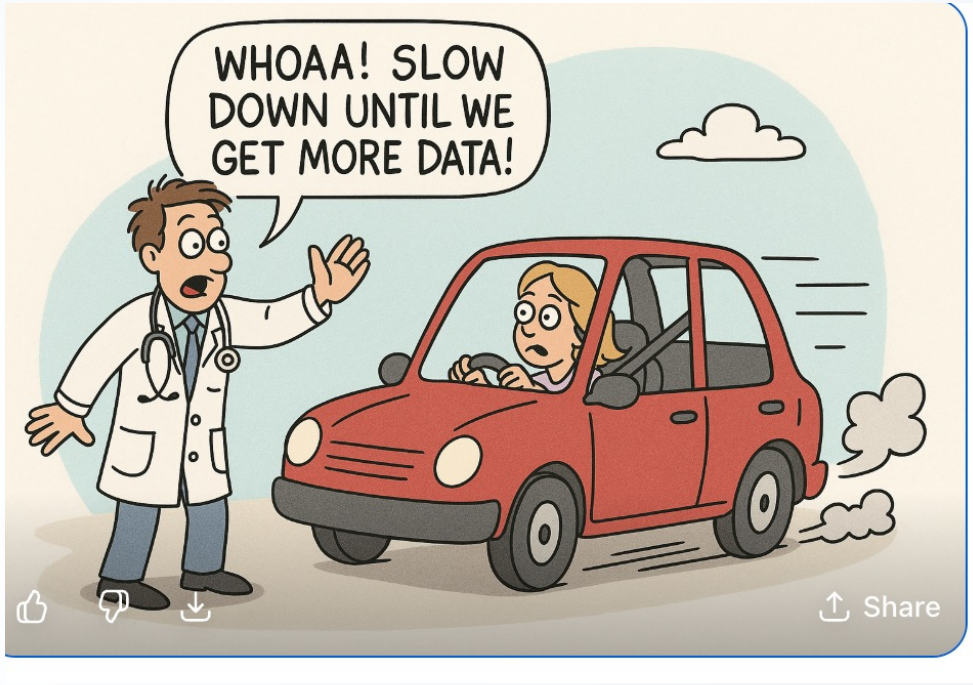
3. Precision Medicine
ctDNA sequencing can detect actionable mutations or resistance pathways, enabling personalized therapy.

EMERGING DATA – PREDICTIVE VALUE/CLINICAL UTILITY

1. Treatment Escalation or De-escalation
ctDNA provides a biologic signal to guide intensity of (neo)adjuvant therapy:

Escalation: Trials like **DARE or PERSEVERE** are investigating if ctDNA-positive patients should receive escalation of targeted therapy and to guide treatment strategy (**PERSEVERE**).

De-escalation: Absence of ctDNA could eventually justify sparing some patients from toxic treatment.



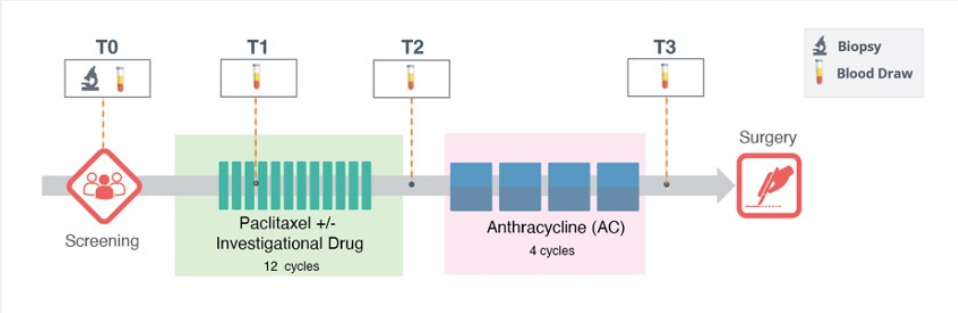
2. Targeted therapies in EBC based on ctDNA sequencing

Which assay to use depends on the clinical setting. It is critical to choose the right test for the right setting.

PROGNOSTIC VALUE: Risk Stratification & MRD Detection

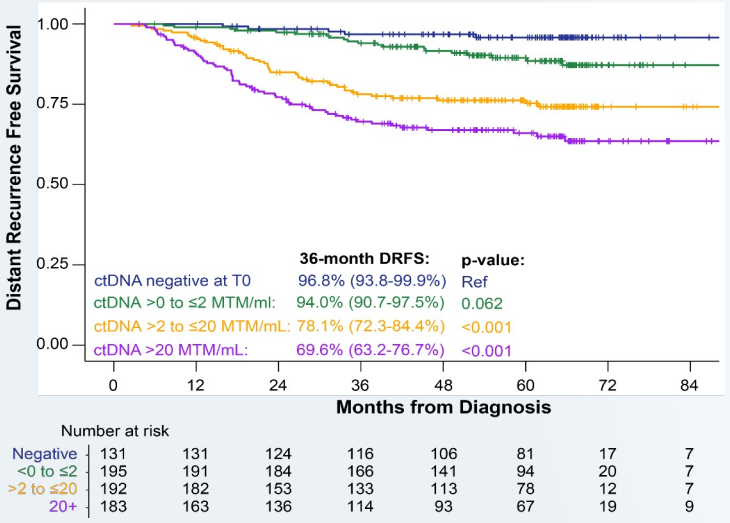
ctDNA at diagnosis and after NACT has prognostic value in patients with early-stage breast cancer

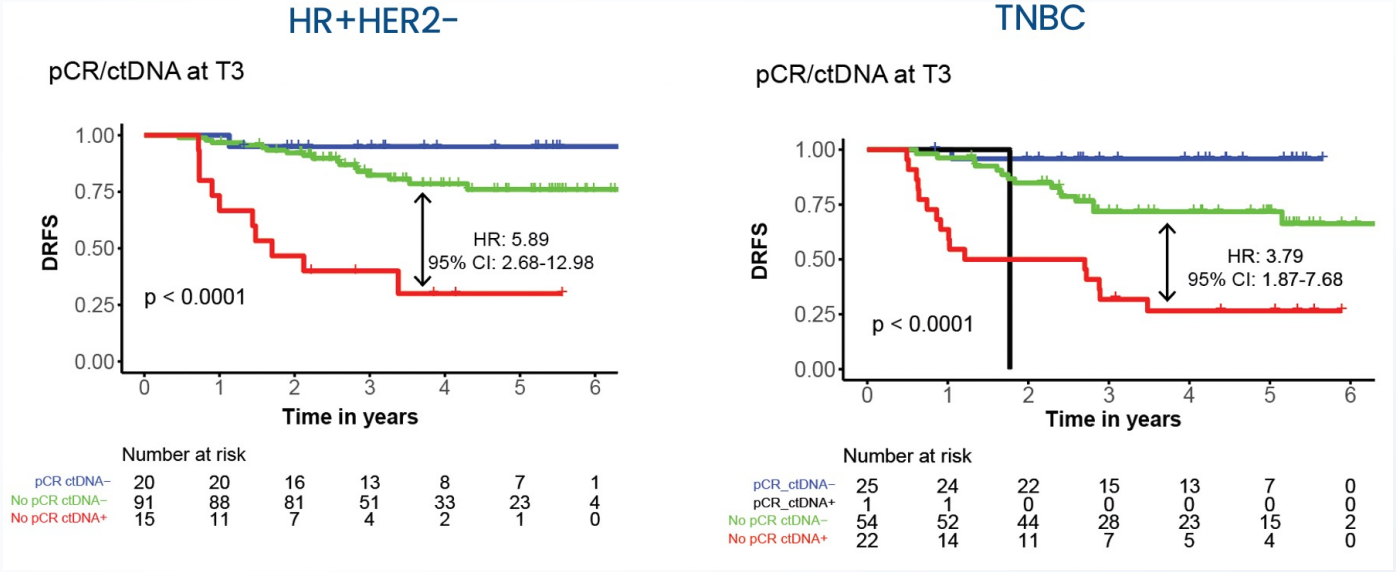
I-SPY2



- Higher ctDNA conc at diagnosis → higher risk
- ctDNA clearance after NACT associated with favorable DRFS
- In pts with residual disease, ctDNA adds additional prognostic value in both TN and HR+/HER2- subtypes

Baseline ctDNA





Magbanua M et al, ESMO Breast 2025

Magbanua et al, Cancer Cell, 2023

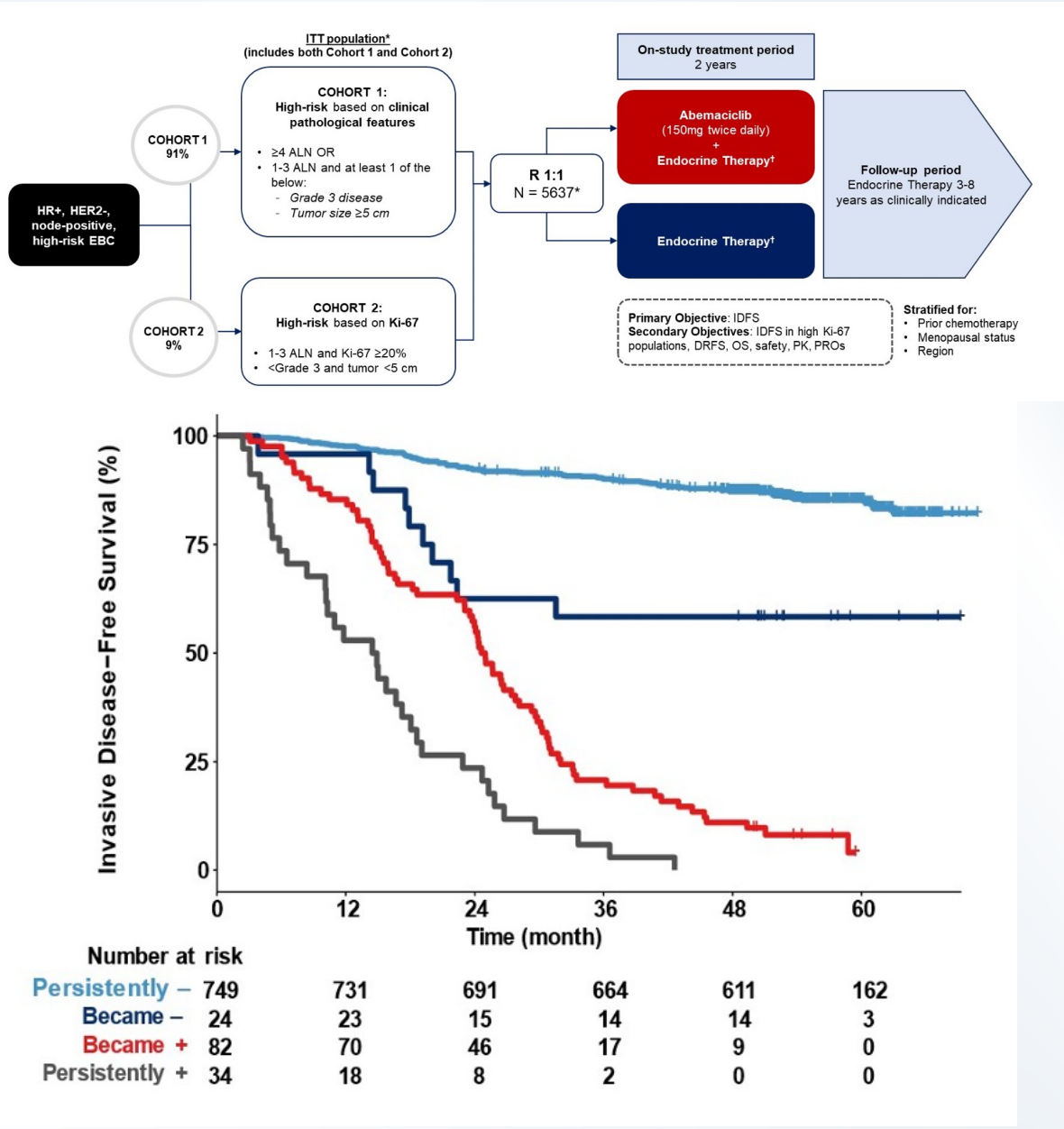
Adapted from Jo Chien, MD

MonarchE: ctDNA cohort

- Pts with +ctDNA at baseline who became negative had better outcomes than pts who did not clear or who became ctDNA+.

- Low incidence of +ctDNA →8% (70/910) in high-risk group
  - Need more sensitive MRD assays, especially for HR+/HER2- subtype

ctDNA cohort (N=910)	ctDNA detection, n (%)
Baseline Negative (–), undetected	840 (92)
Persistently –	749/831* (90)
Became +	82/831* (10)
Baseline Positive (+), detected	70 (8)
Persistently +	34/58** (59)
Became – (undetected)	24/58** (41)



Loi S et. Al, ASCO 2024

Adapted from Jo Chien, MD

CLINICAL UTILITY: PROSPECTIVE THERAPEUTIC STUDIES

Prospective therapeutic trials guided by ctDNA in EBC

TNBC

cTRAK-TN – Pembrolizumab vs Observation 27% +ctDNA, 72% w/ mets
ZEST – Niraparib vs Placebo 8% +ctDNA, 50% w/ mets → closed early
ASPIRA – Sacituzumab + Atezolizumab (single arm)
PERSEVERE – Capecitabine vs Talazoparib vs Atezolizumab vs Inavolisib
ARTEMIS – Capecitabine vs Capecitabine + Camrelizumab + Apatinib

HR+/HER2-

DARE – Fulvestrant+Palbociclib vs ET Interim Analysis 1: 9% +ctDNA, 27% with mets
LEADER – ET+ Ribociclib vs ET
TRAK-ER – Fulvestrant + Palbociclib vs ET
TREAT – Elacestrant vs. ET

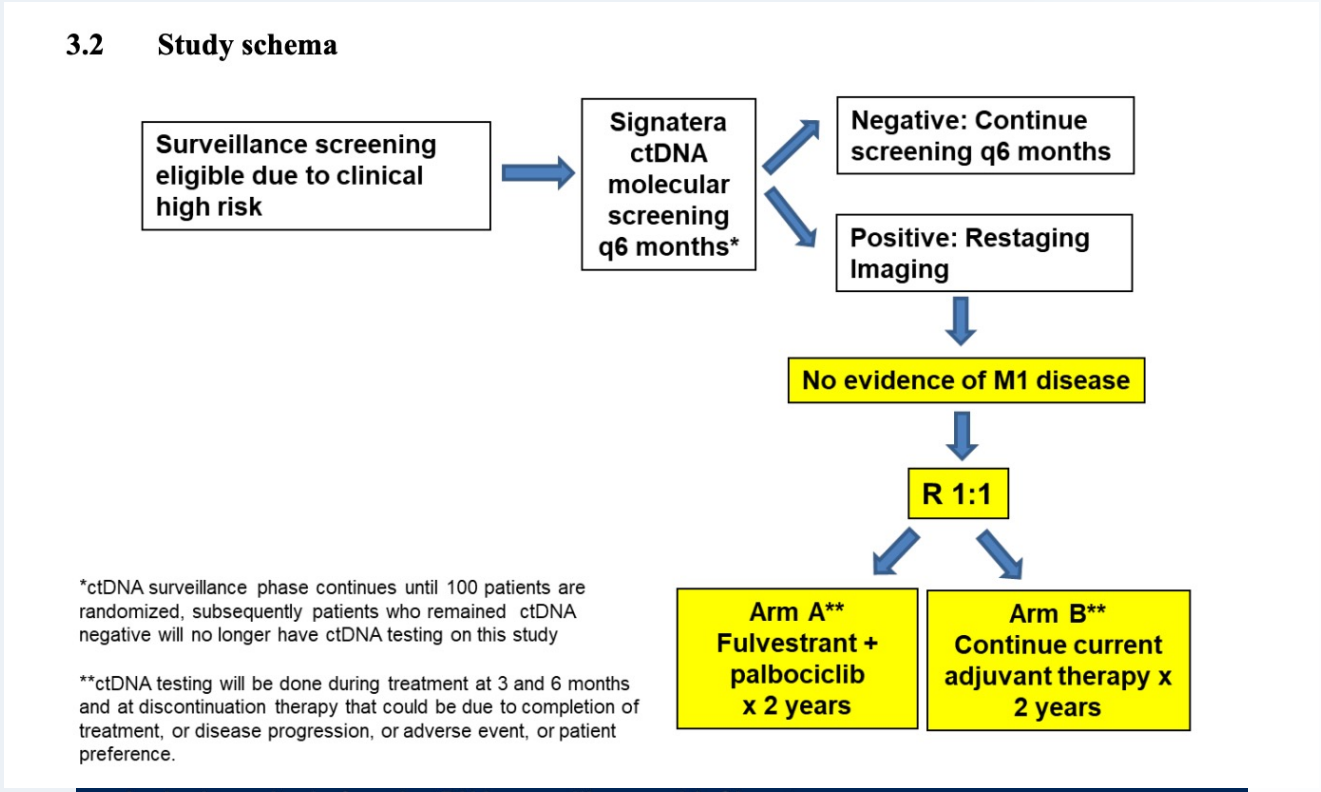
HER2+

KAN-HER2 – Neratinib+TDM-1 (single arm)

Adapted from Jo Chien, MD

Slide adapted from David Cescon

DARE Study



Inclusion criteria for q6 ctDNA surveillance with Signatera assay:

Patients receiving adjuvant ET for >6 months (mo) but <7 years, with either:

- (i) recurrence risk >15% (PREDICT, RSPC, CTS5)
- (ii) >4 positive axillary lymph nodes
- (iii) primary tumor >5 cm, or 1-3 positive nodes with grade 3 histology, or >3 cm tumor, or high molecular risk (Oncotype Dx RS >26, MammaPrint high risk, EndoPredict >4, Prosigna score >60)

ctDNA+ patients underwent systemic staging with imaging

If imaging negative, patients were randomized to continuation of adjuvant therapy v.s. switching to fulvestrant + palbociclib

- This study shows the feasibility of a randomized ctDNA-directed interventional trial in ER+/HER2- patients during follow-up.
  - 12% of patients were found to be ctDNA+ during surveillance
  - 71% of ctDNA+ patients were imaging negative for metastatic disease (i.e. had molecular relapse)
  - 93% of patients with molecular relapse were willing to be randomized
- Interim analysis revealed higher clearance in Arm A compared to Arm B.
- **On-treatment ctDNA dynamics were prognostic of patient outcomes.**

Adapted from Lajos Pusztai, MD

Where Do We Go From Here?

- Involves a balanced discussion with the patient on prognostic implications and what we know about clinical utility thus far.
  - Benefit: prognostic value (>>> tumor markers)
  - Costs: $$, increased diagnostic testing/procedure, patient anxiety, potential therapeutic toxicity without clinical benefit
- Can treatment of MRD meaningfully delay or prevent clinical relapse?
- Currently—most appropriate clinical utility is on trial

ctDNA in Early-Stage Breast Cancer

What is ctDNA?

- ctDNA is tiny fragments of cancer DNA found in the blood.
- It comes from cancer cells that have died, even after their DNA into the bloodstream.
- A simple blood test (sometimes called a "liquid biopsy") can look for ctDNA.

Why is ctDNA Important?

- It may help find cancer before it shows up on scans.
- It can tell us if cancer is still active, even after surgery and treatment
- Doctors can watch for cancer coming back by checking your blood over time.

How ctDNA May Help You

1. **Personalized Monitoring:** Tracks your unique cancer's DNA.
2. **Early Warning:** May detect a recurrence before symptoms or imaging
3. **Guides Treatment:** in the future, it might help decide if more treatment is needed—or not

What Patients Should Know

- ctDNA testing is still new and mostly used in clinical trials.
- It does **not** replace mammograms or other scans.
- A positive ctDNA test doesn't always mean—the cancer is back—but it means your care team will watch closely

Is ctDNA Testing Right for Me?

- It may be offered if you've had high-risk early breast cancer
- Your oncologist may discuss ctDNA testing if you're part of a clinical trial.

Jing Xi et al. *JCO Oncol Pract* **20**, 1460 1470(2024).DOI:10.1200/OP.24.00274

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