2026

DEBATES AND DIDACTICS in Hematology and Oncology

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Where Science Becomes Hope

JULY 23-26, 2026 • SEA ISLAND, GEORGIA

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The Role of ctDNA in the management of Early-Stage Breast Cancer

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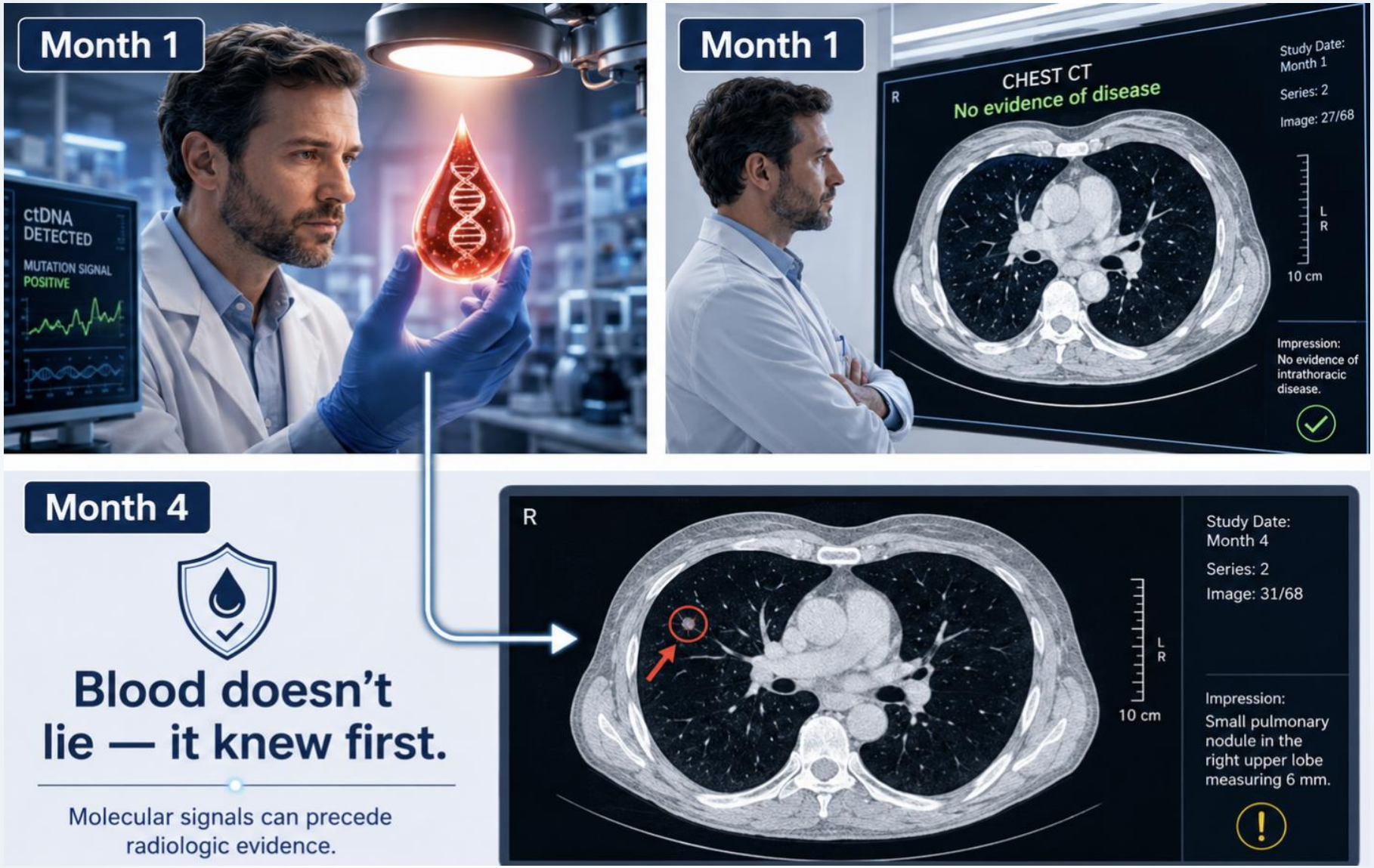
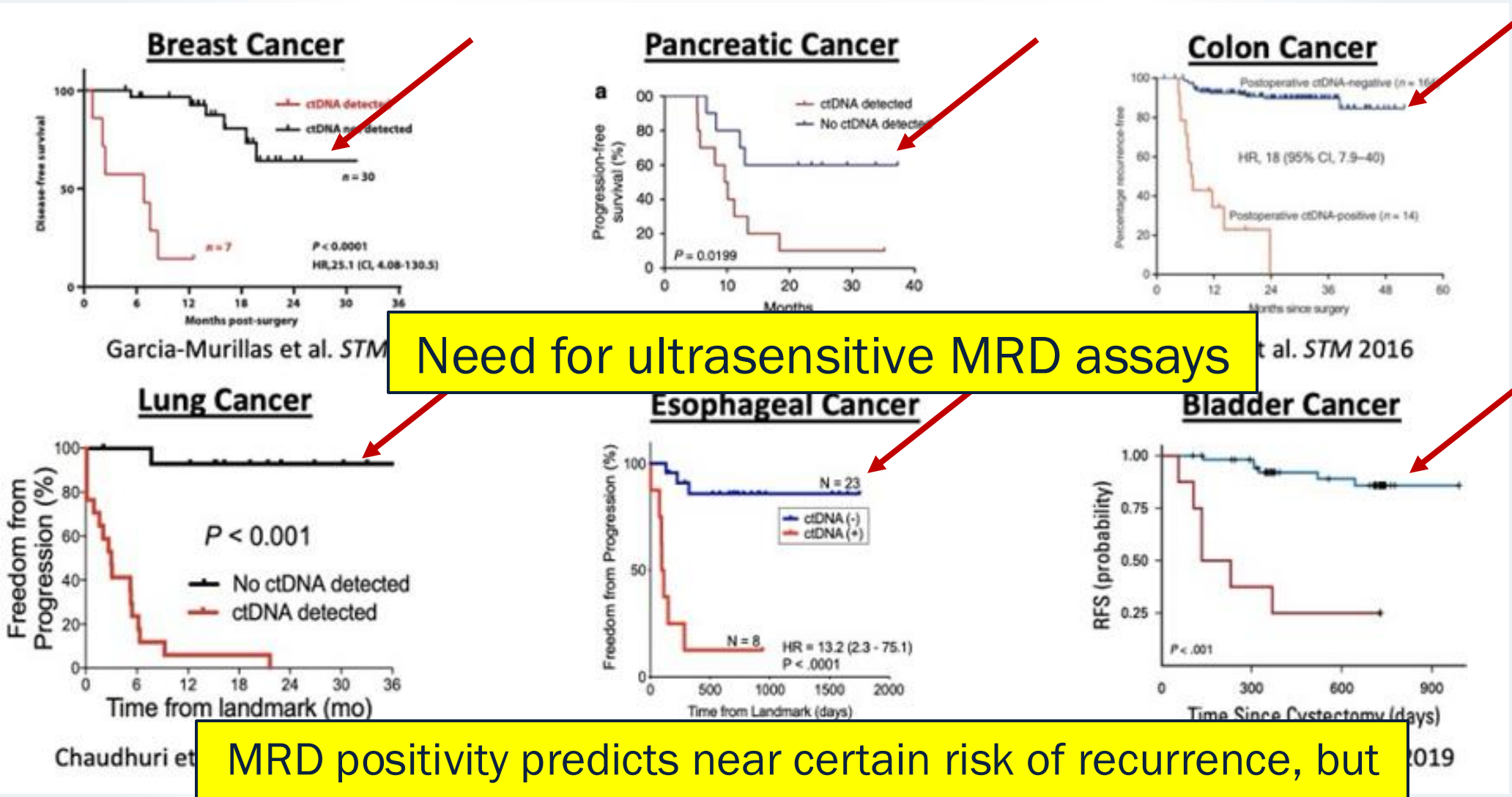
Director, Breast Translational Research

Winship Cancer Institute of Emory University

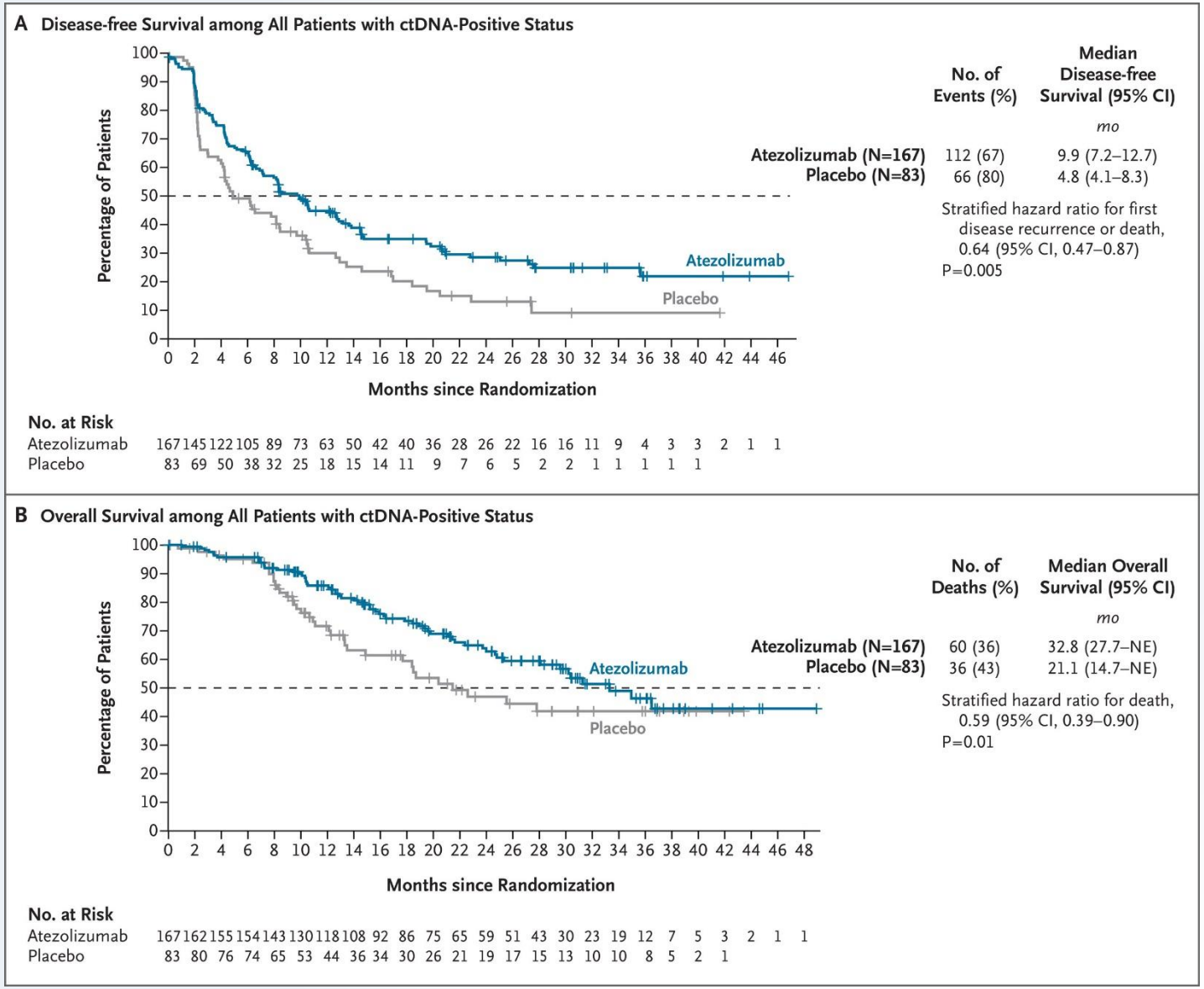
The Blood Does Not Lie – But Should We Act ?



ctDNA MRD is an extremely strong prognostic biomarker across early-stage solid tumors



ctDNA MRD-guided adjuvant IO in bladder cancer



- **IMvigor011**, randomized, double-blind, placebo-controlled trial
- 250 patients with MIBC post curative-intent surgery
- ctDNA MRD positive by serial evaluation starting 6 weeks after cystectomy and during the subsequent 12 months
- Disease-free survival benefit of 9.9 months for atezolizumab vs. 4.8 months in the placebo arm
- Overall survival benefit of 32.8 months vs. 21.1 months in the placebo arm

The FDA approved atezolizumab as adjuvant therapy for MIBC guided by ctDNA minimal residual disease (Signatera CDx) on May 15, 2026.

Powles et al., *Nature*, 2021, Powles et al., *NEJM*, 2025; *Anagnostou V, ASCO 2026*

Patient Case

42-year-old female diagnosed with cT2N1 grade 3 invasive ductal carcinoma of the breast, HR positive, HER2 negative has completed neoadjuvant chemotherapy with ddACT, surgery shows 2 cm residual disease with 3/14 lymph nodes involved with disease. After completing radiation, she is planned to receive OFS + AI + ribociclib + zolendronic acid. She is interested in learning more about ctDNA surveillance and asks:

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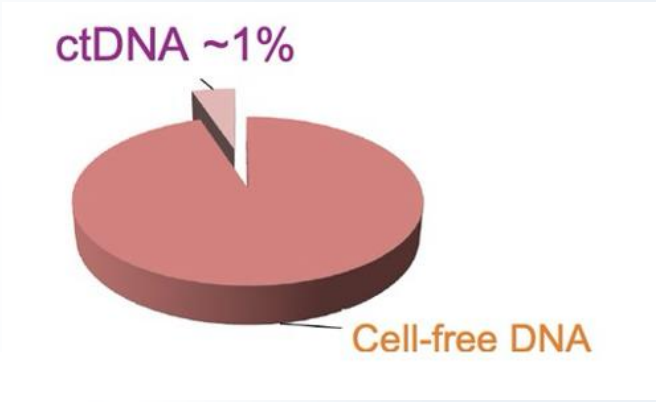
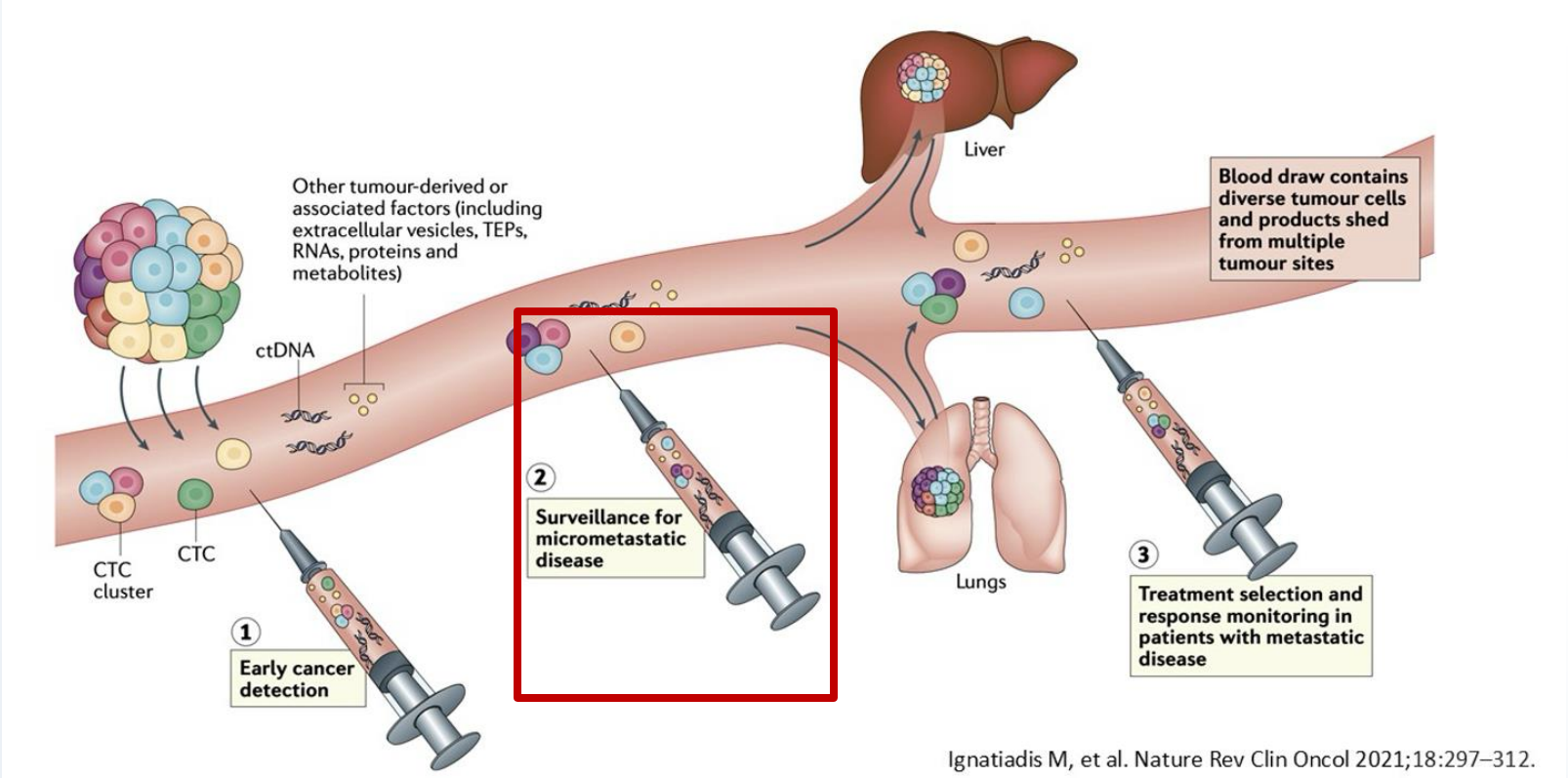
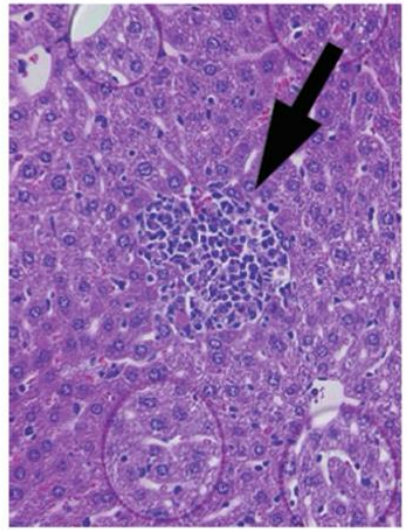
What are cfDNA and ctDNA and where do they come from ?

- cfDNA is the total amount of DNA in the circulation
- ctDNA is a subset (≅1%) of cfDNA shed by the tumor cells
- ctDNA half-life is minutes to hours



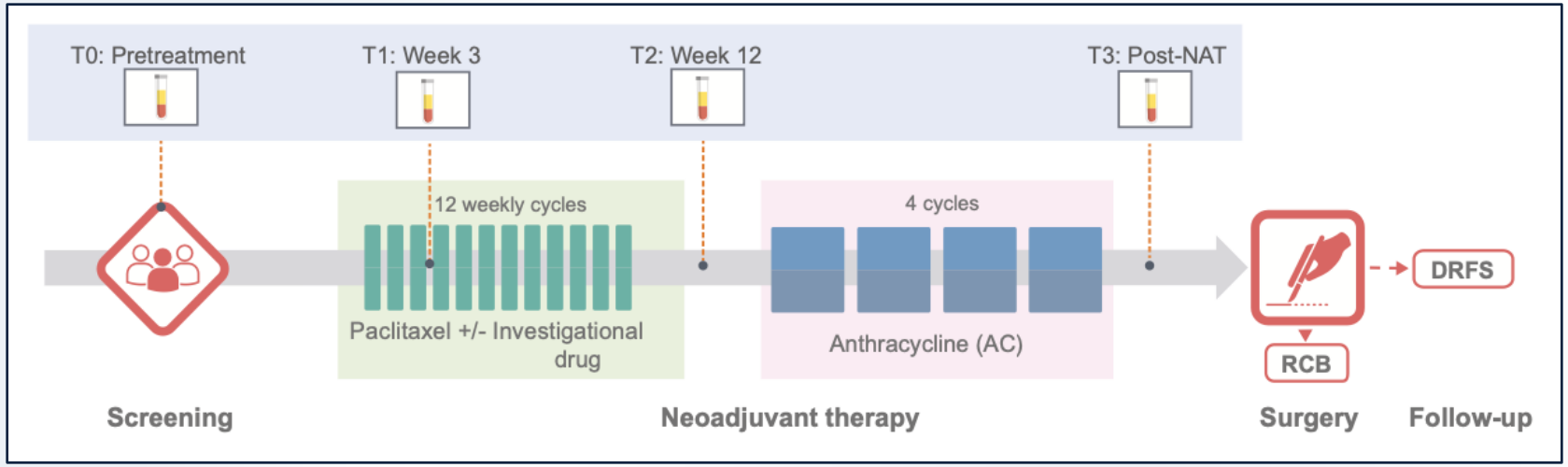


Ignatiadis M, et al. Nature Rev Clin Oncol 2021;18:297–312.

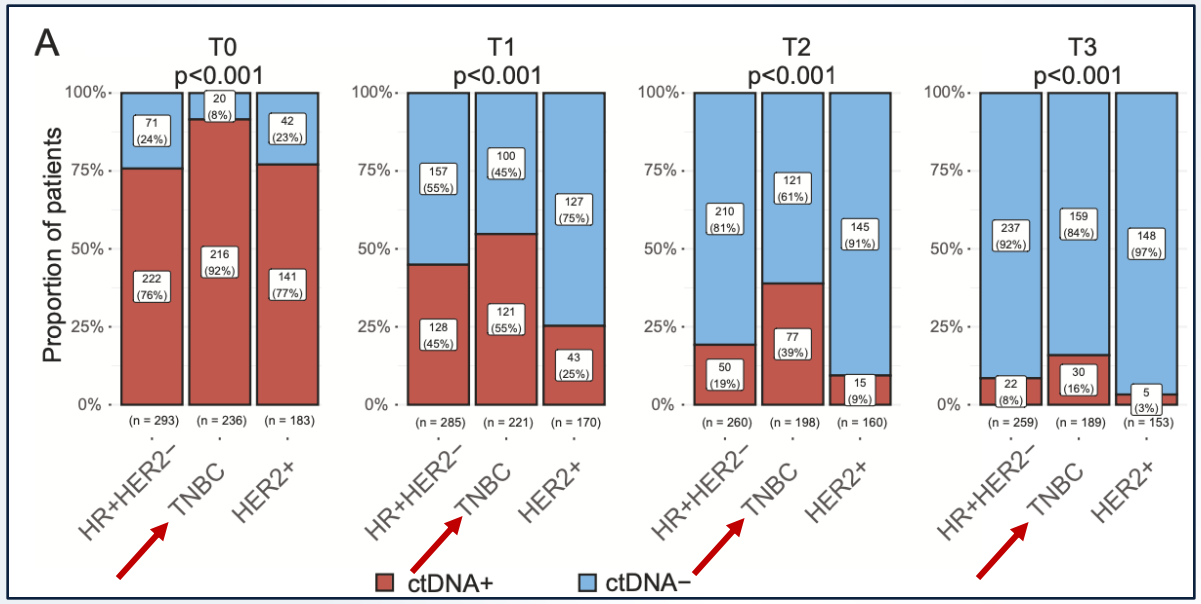


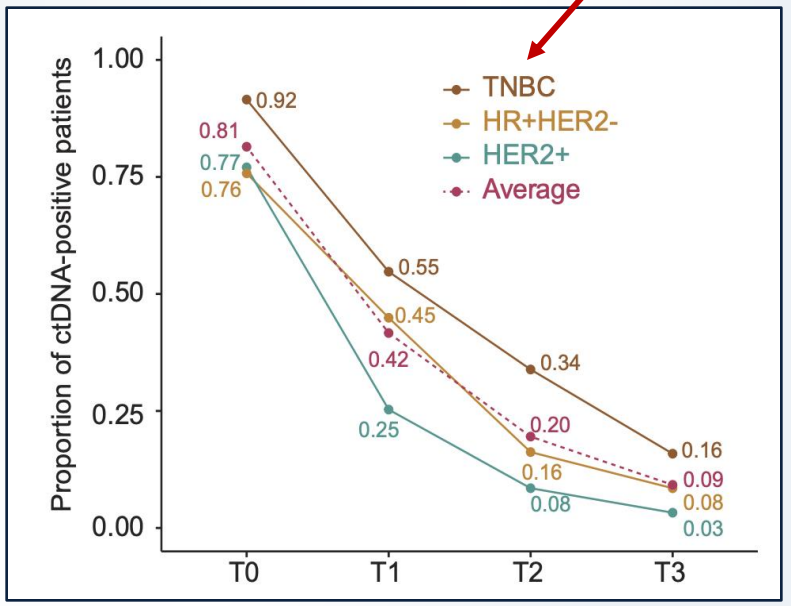
Small volume of tumor cells remaining after treatment in patients with no clinical evidence of disease.

TNBC has the highest ctDNA shedding among breast cancer subtypes



T0 - pretreatment
T1 - week 3
T2 - week 12
T3 - post-NAT

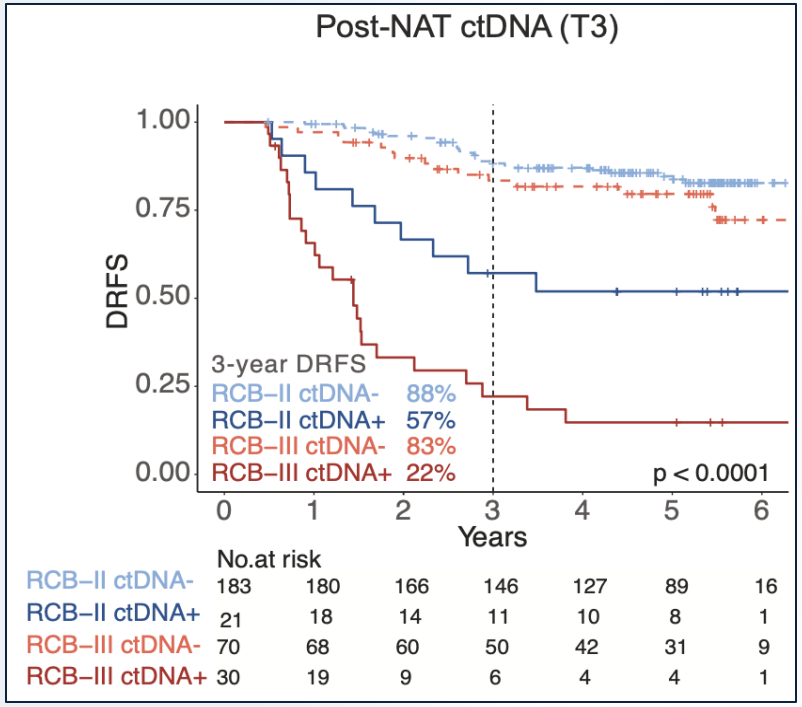


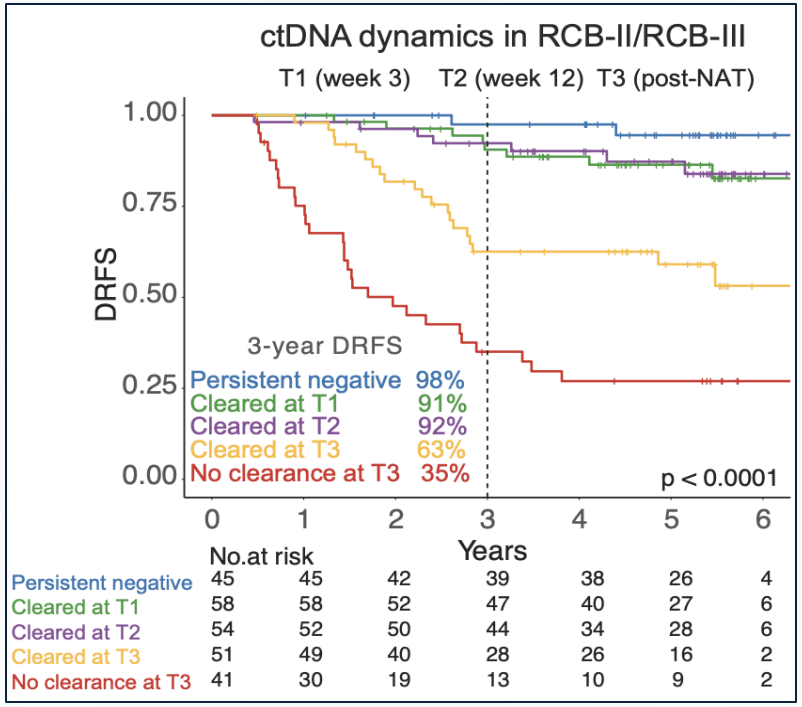


Magbanua MJM, Nature Communications 2025

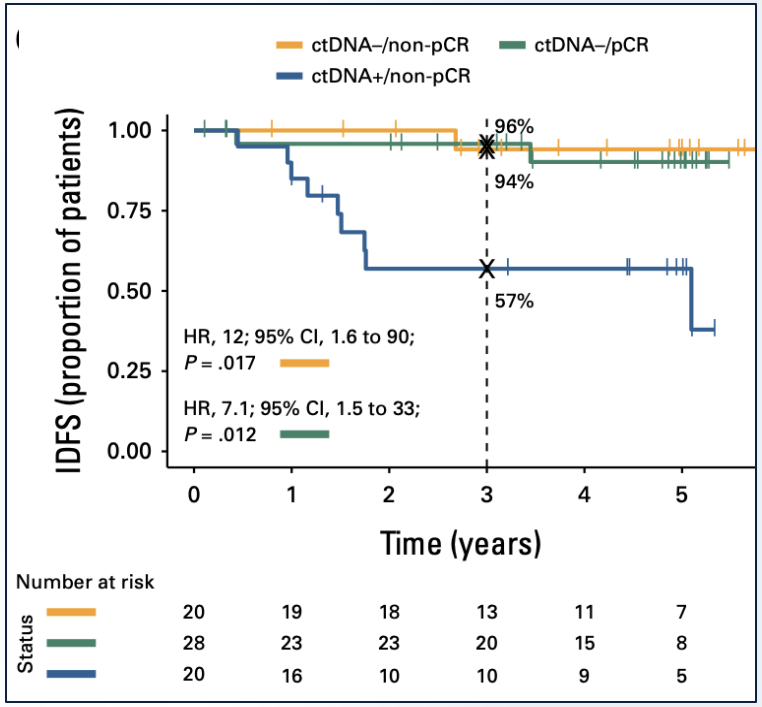
ctDNA is prognostic and improves on RCB for risk stratification

ISPY2 (Signatera Exome)





PREDICT-DNA (Personalis NeXT)

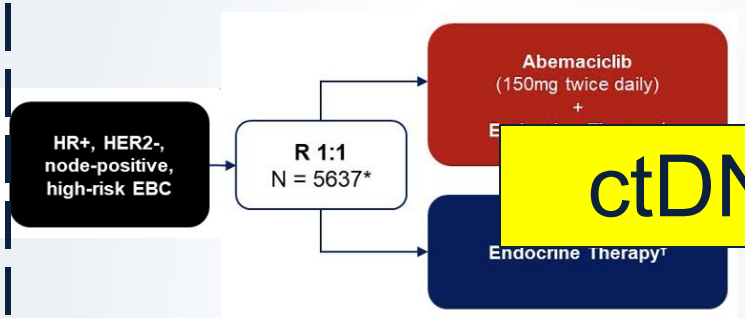


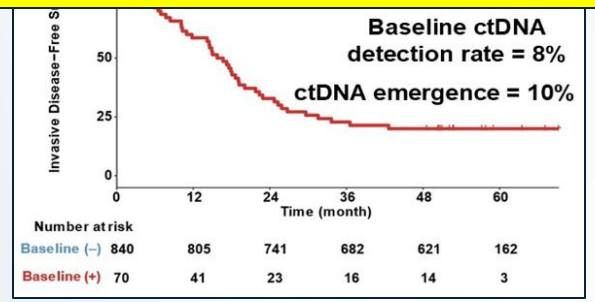
Magbanua MJM, et al. Nature Communications 2025; Hunter NB, et al. JCO 2026

High risk ER+ breast cancer: Retrospective analysis of ctDNA

monarchE

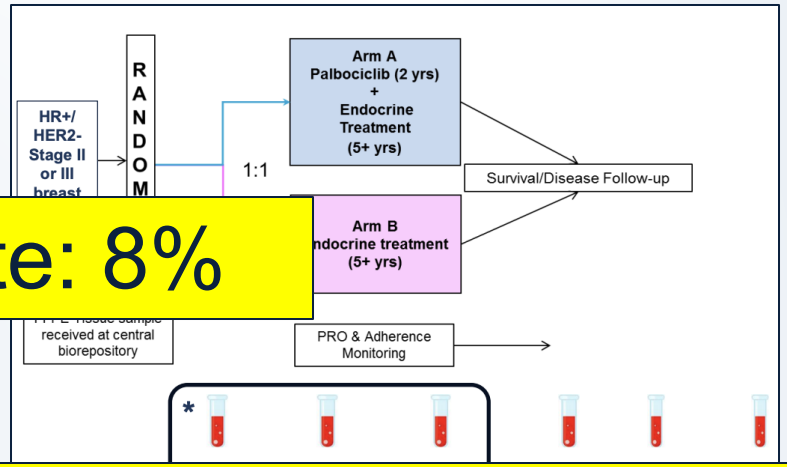
Signatera Exome

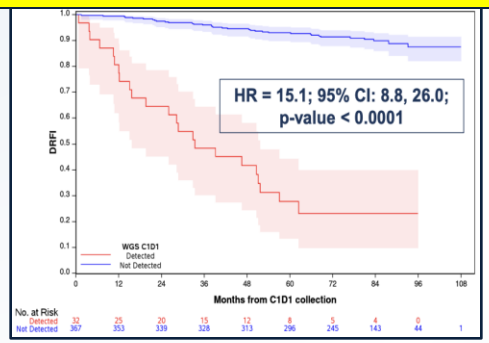


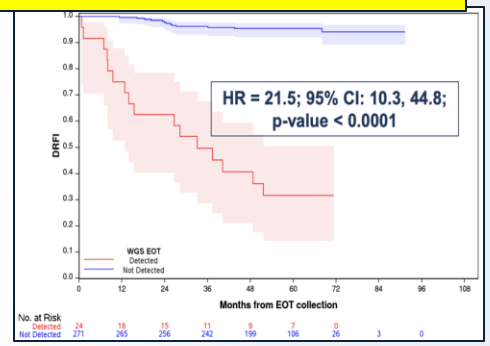


PALLAS

Signatera Genome







ctDNA detection rate: 8%

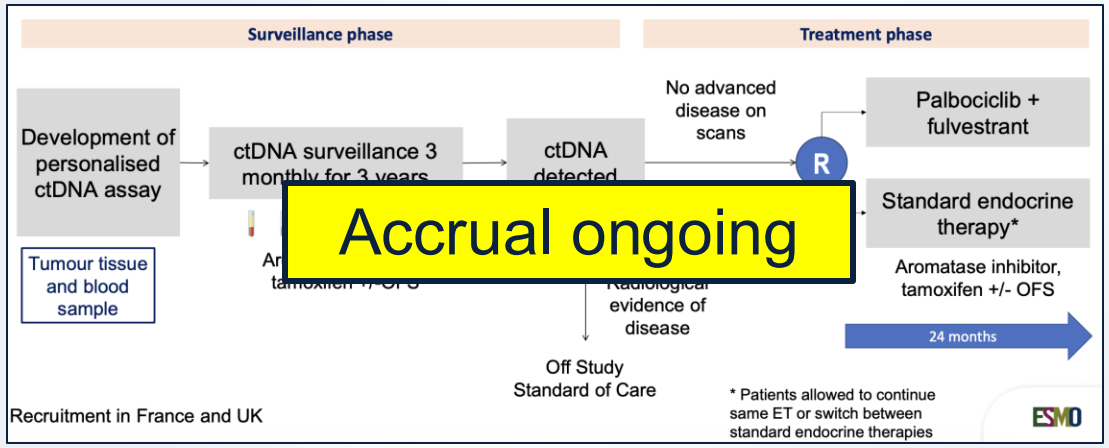
What about ctDNA guided interventional clinical trials ?

Loi S, et al. ASCO 2024; Parsons H, et al. SABCS 2025

ctDNA+ 11%, metastatic diagnosis at first ctDNA+ 27% to 43%

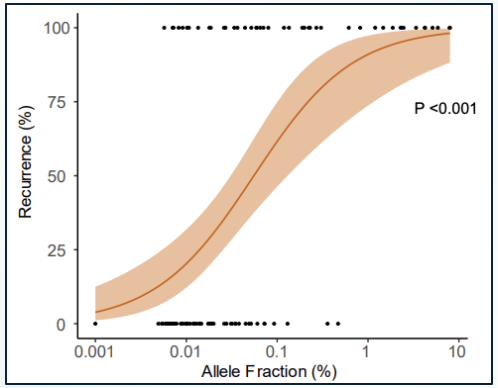
TRAK-ER

Plasma Detect ID Assay



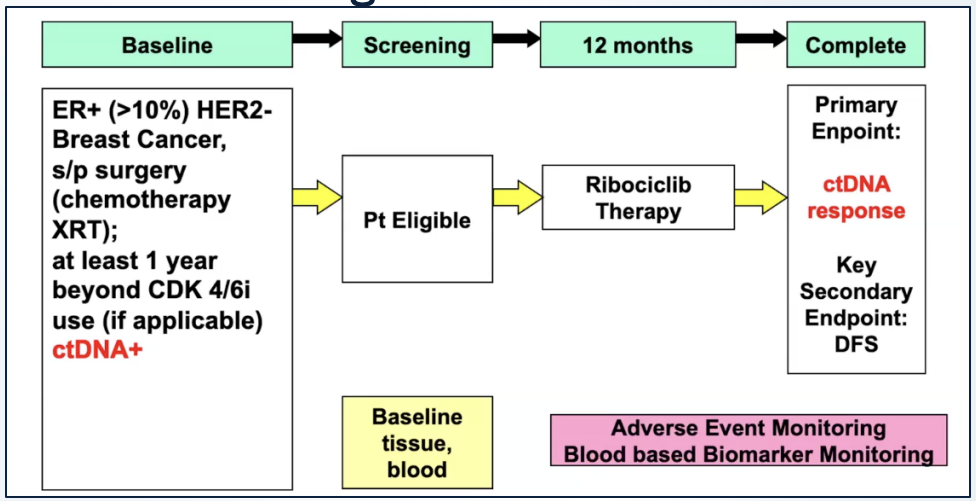
ctDNA+ : 11.6% (105/901)

42.3% metastatic disease (45/105)



LEADER

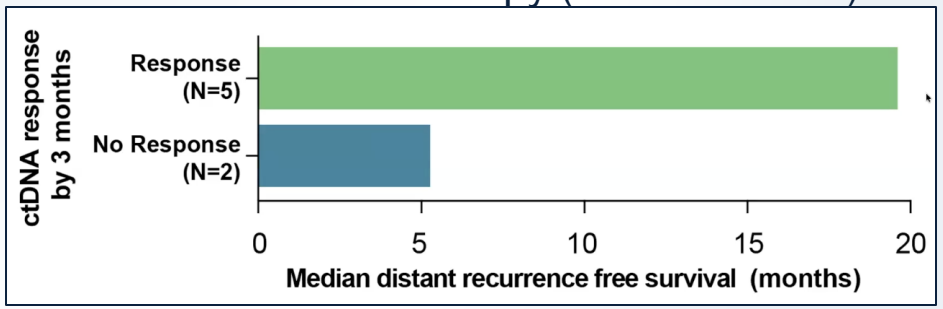
Signatera Exome



ctDNA positivity rate: 11% (15/140)

27% metastatic disease (4/15)

10 initiated therapy (ribociclib + AI)



Medford A, et al. SABCS 2025

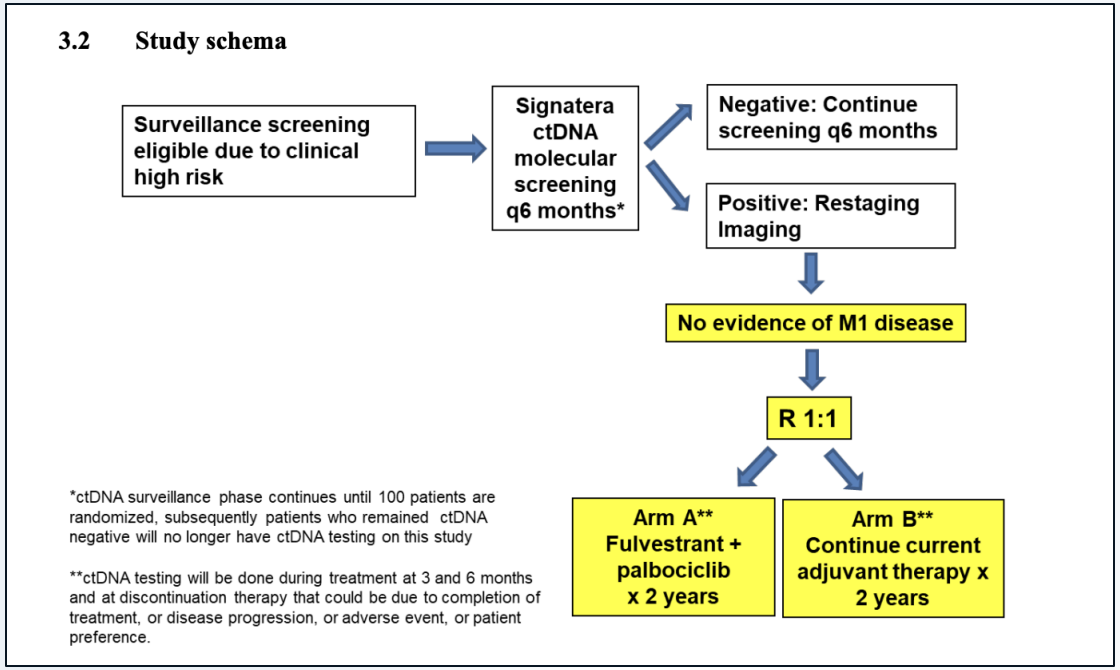
Higher clearance → No relapse

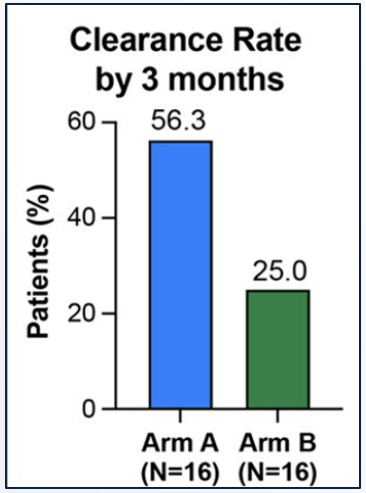
DARE

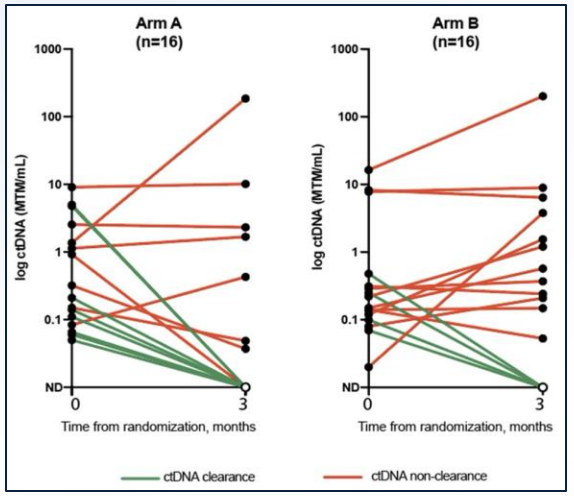
Signatera Exome

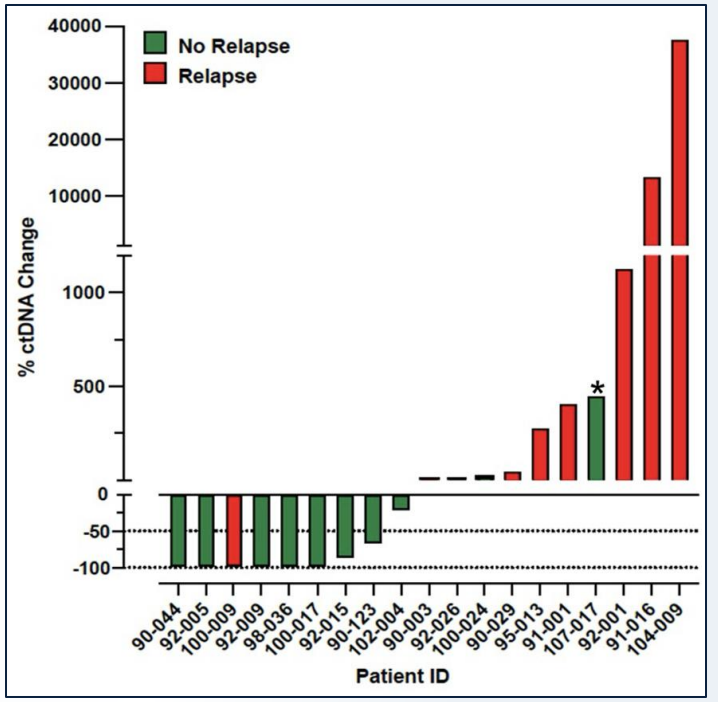
ctDNA detection: 12%

High-risk HR+ on adjuvant ET >6 months and <7 years









1 of 9 patients with ctDNA clearance or decrease at 3 months post-randomization and RFS data available had clinical relapse

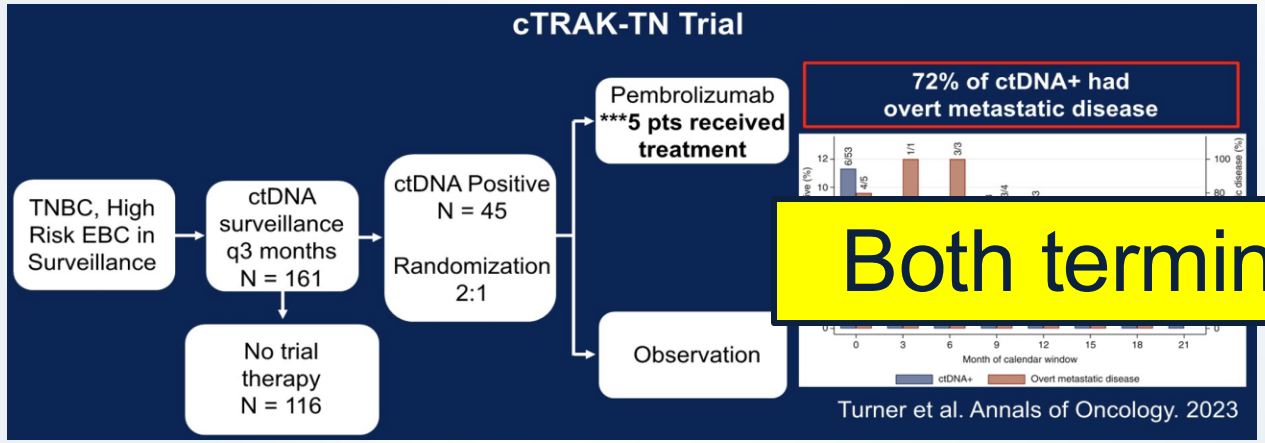
6 of 10 patients with increasing ctDNA levels had clinical relapse

Accrual ongoing

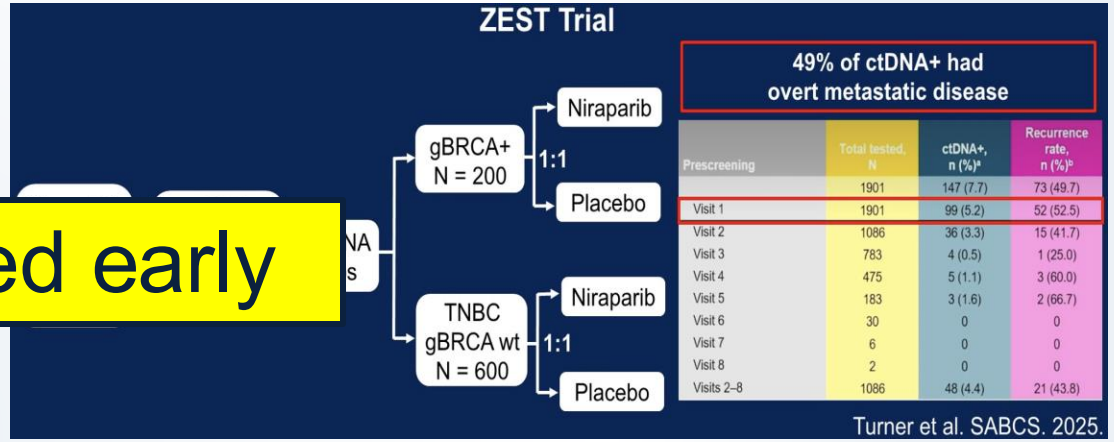
Pusztai L, et al. ASCO 2025

TNBC and BRCAm HER2-negative: ctDNA+ 8-14%, metastatic diagnosis at first ctDNA+ 49-72%

digital droplet PCR: 14% ctDNA+



Signatera Exome: 8% ctDNA+



Both terminated early

RFS 11.4 vs. 5.4 months; HR 0.64, 95% CI 0.30-1.39

Challenges with the clinical trial

- Low rate of ctDNA positivity
- High rate of metastatic disease at ctDNA detection

- Select relatively high-risk patients
- Test as early as possible from completion of standard therapy, and improve sensitivity of ctDNA testing to maximize lead time between molecular and clinical recurrence

Cobain E, ASCO 2026

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What is the likelihood this test would be positive and if positive, does it mean my cancer will come back – if yes, how soon ?

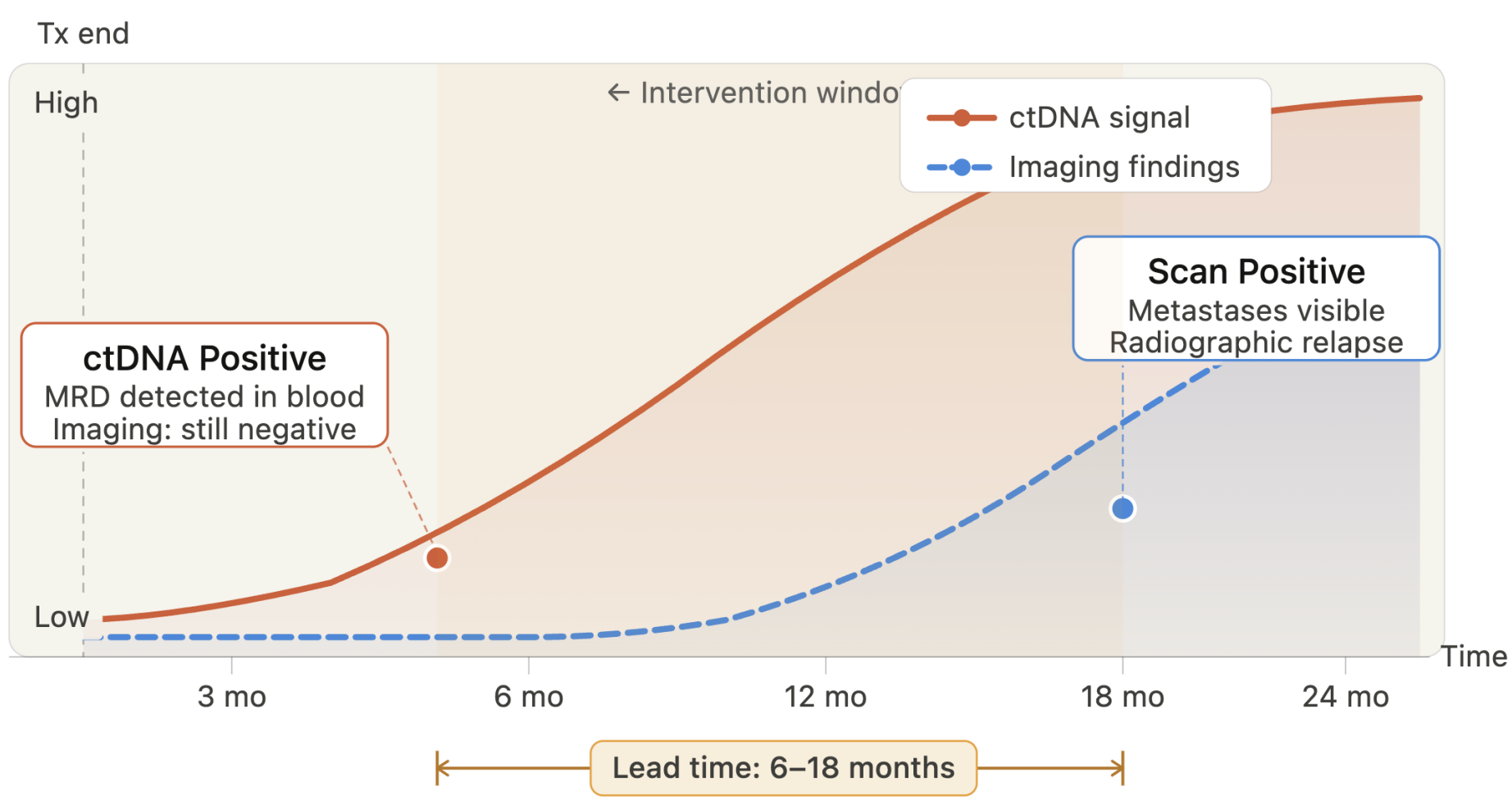
Trial	Design	Subtype	Test	% ctDNA positive
PALLAS	Retrospective	HR+/HER2-	Signatera Genome	8%
CHiRP	Retrospective	HR+/HER2–	RaDaR	10%
MonarchE	Retrospective	HR+/HER2–	Signatera Exome	8%
ZEST	ective	TNBC or BRCA+ HR+	Signatera Exome	8%, >50% recurrent
TRAK-TN	Prospective	TNBC	Digital pCR	14%, >70% recurrent
DARE	Prospective		Signatera Exome	12%, 30% recurrent
LEADER	Prospec		Signatera Exome	11%, 27% recurrent
TRAK-ER	Prospective		Plasma Detect ID	12%, >40% recurrent

Less sensitive ctDNA assay

Different biology: luminal and TNBC, window of opportunity longer for indolent tumors

Mayer E, et al. ESMO Breast 2026

What is the likelihood this test would be positive and if positive, does it mean my cancer will come back – if yes, how soon ?



Schlam I et al, JAMA Oncology 2026

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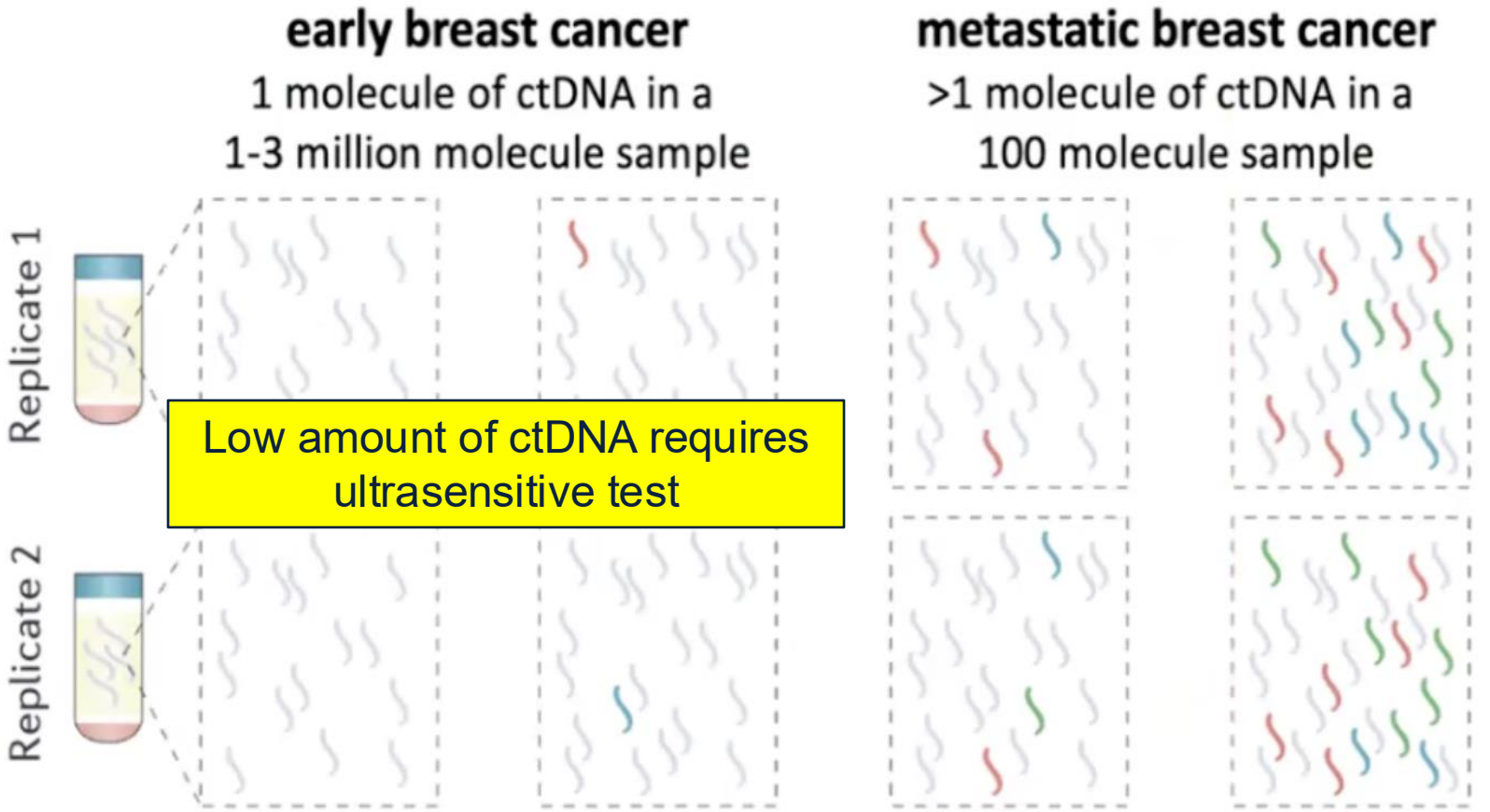
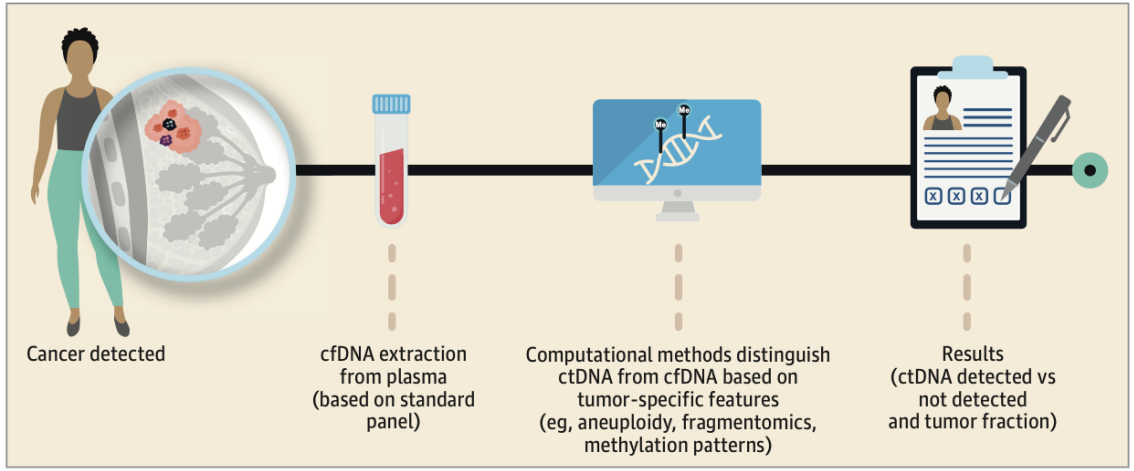
Challenges of detecting minimal residual disease



Slide courtesy: Moganti S, Dana Farber Cancer Institute

Tumor-agnostic vs. tumor-informed ctDNA detection platforms

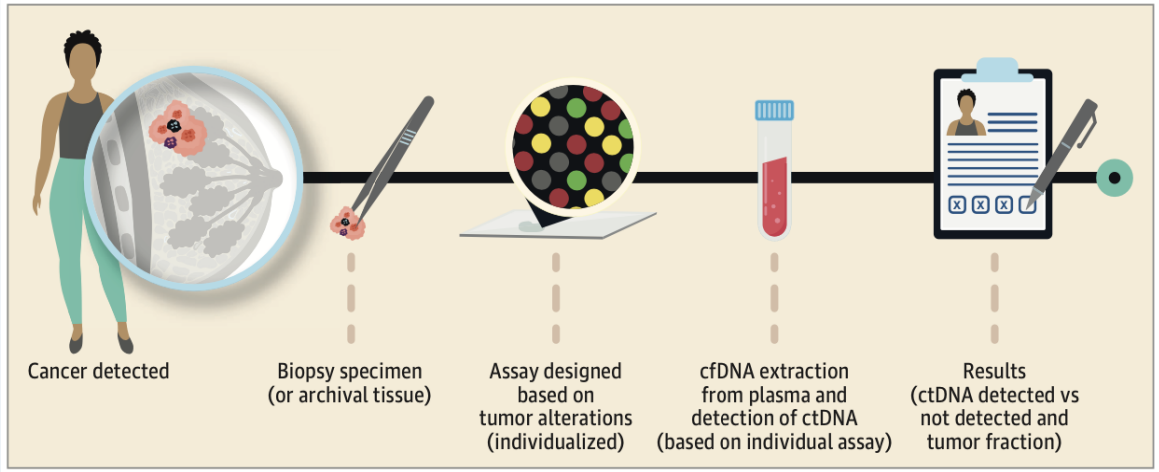
Tumor-Agnostic



Pros	Cons
Primary tumor analysis not needed	Less sensitive
Quick turn-around, lower cost	Less specific
Detects acquired mutations	
Fragmentatio analysis possible	

"Generic"

Tumor-Informed (Bespoke)

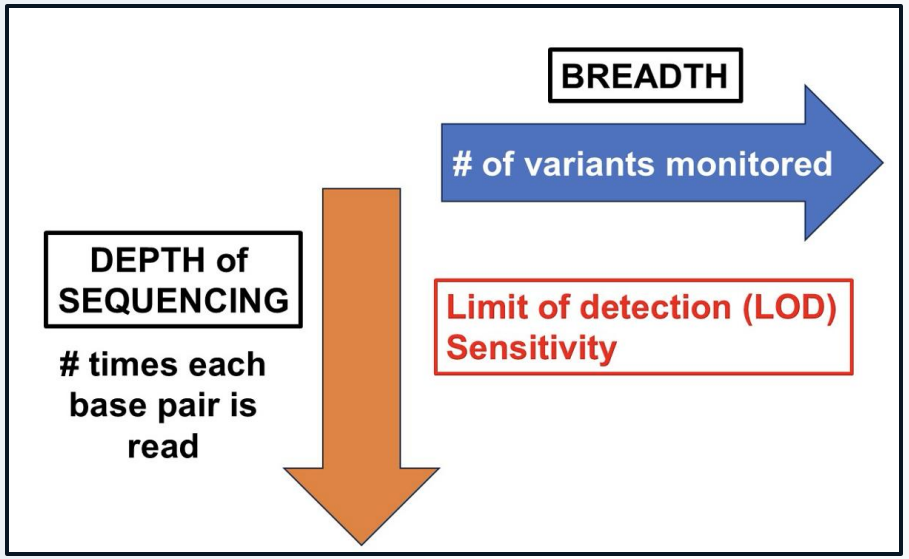


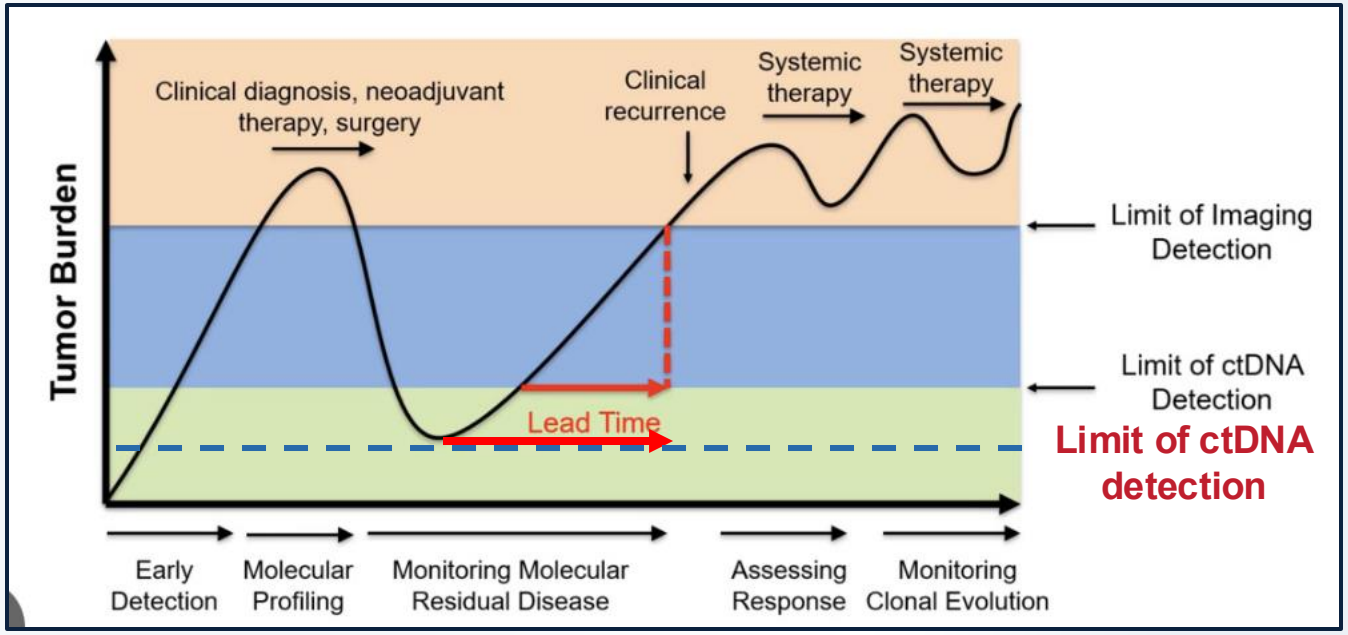
Pros	Cons
More sensitive	Time consuming, higher cost
More specific	Do not capture emergent mutations

"Personalized"

Chien J, ASCO 2026; Schlam I et al, JAMA Oncology 2026

ctDNA sensitivity is built on breadth and depth





Chien J, ASCO 2026; Schlam I, JAMA Onc 2026; Landon et al, Nat Med 2025

ctDNA sensitivity is built on breadth and depth of the assay

	Type of assay	# variants	LOD
NeXT Personal (Personalis)	WGS	1800	3.45 ppm
Signatera Genome	WGS	64	5-9 ppm
Pathlight (SAGA)	WGS	16	5 ppm (0.0005%)
Exact Sciences	WES	50 – 200	50 ppm (0.005% TF)
RaDaR (NeoGenomics)	WES	48	11 ppm (0.0011% VAF)
Signatera Exome	WES	16	100 ppm (0.01% VAF)
Foundation One Tracker	CGP-based	2 – 16	>97.3% at ≥5 MTM/mL
Guardant Reveal	Plasma-based		0.01%

Schlam I et al, JAMA Oncology 2026

Assay Choice Changes What We Detect

cTRAK-TN

	WES-informed assay (RaDar)	Digital PCR testing
MRD during surveillance	47.9%	0%
Median lead time	6.1 months	3.9 months

ChemoNEAR

	WGS-based assay (NexT Personal)	WES-based assay	Digital PCR
Pre-NAT	100%	84%	76%
Median lead time	15.6 months	10.2 months	-

WGS > WES > digital PCR

Schlam I, JAMA Oncol 2026; Turner N et al. Ann Oncol 2023; Coakley M et al., CCR 2024; Garcia-Murillas et al, Ann Oncol 2025

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Examples of Ongoing Interventional Clinical Trials

	PREDICT-RD (TBCRC-071)	Treat ctDNA
Population	High risk TNBC with RCB II/III after NAT (N = 78)	High risk HR+ HER2− EBC on adjuvant ET for 4.5–7 years (N = 1960 surveillance)
ctDNA monitoring	Q6 weeks during adjuvant systemic therapy Q3 months thereafter	Q6 months during surveillance Week 4, 16 and then every 4 months during treatment
Assay	Signatera Genome	Signatera Exome
Interventions for ctDNA+	Datopotamab Deruxtecan (Dato-DXd) for 8 cycles	Standard ET vs. Elacestrant for 24 months
Primary Endpoint	Proportion of pts with MRD Key secondary: RFS, OS	Distant metastasis free survival

Prospective ctDNA-guided studies will screen 10x pt population

Study	Setting	Population	~5yr DDFS, intervention arm	Population at residual risk
APHINITY[1]	HER2+	n=4,805	92.5%	7.5% (n=360)
monarchE[2]	HR+/HER2-	n=5,637	86%	14% (n=789)
KEYNOTE 522[3]	TNBC	n=1,174	81.3%	18.7% (n=220)

"Where ctDNA fits in this treatment landscape"

1.Von Minckwitz G, et al. *NEJM.* 2017.
2.Johnston TM, et al. *Lancet Onc.* 2023.
3.Schmid P, et al. *SABCS.* Dec 2023.

Von Mincwitz G, et al. NEJM 2017; Johnston TM, et al. Lancet Onc 2023; Schmid P, et al, SABCS Dec 2023; Parsons H, ESMO Breast 2026

ctDNA Has Clinical Validity, Utility Is Still Being Proven

✓ **Confirmed clinical validity:** ctDNA+ strongly prognostic for recurrence

? **Unconfirmed clinical utility:** Does identification of molecular relapse allow modulation of therapy to reverse recurrence ?

Mayer E, ESMO Breast 2026

Some Ongoing Trials Investigating Clinical Utility of ctDNA testing

Escalation after ctDNA positivity

Trial	Population	MRD Assay	Intervention	Primary End Point
DARE (NCT04567420)	HR+ / ERBB2–, high-risk, on ET	Signatera Exome	Fulvestrant + palbociclib vs continuation of ET	RFS
LEADER (pt 2) (NCT03285412)	HR+ / ERBB2–, on ET ≥1 yr remaining	Signatera Exome	Ribociclib + AI for 1 yr	12-mo ctDNA clearance
TRAK-ER (NCT04985266)	HR+ / ERBB2–, up to 7 yr on ET	Invitae personalized	Standard ET vs palbociclib + fulvestrant	RFS
TREAT-ctDNA (NCT05512364)	HR+ / ERBB2–, 4.5–7 yr on ET	Signatera Exome	Standard ET vs elacestrant for 24 mo	Distant metastases-free survival

Post-neoadjuvant residual disease

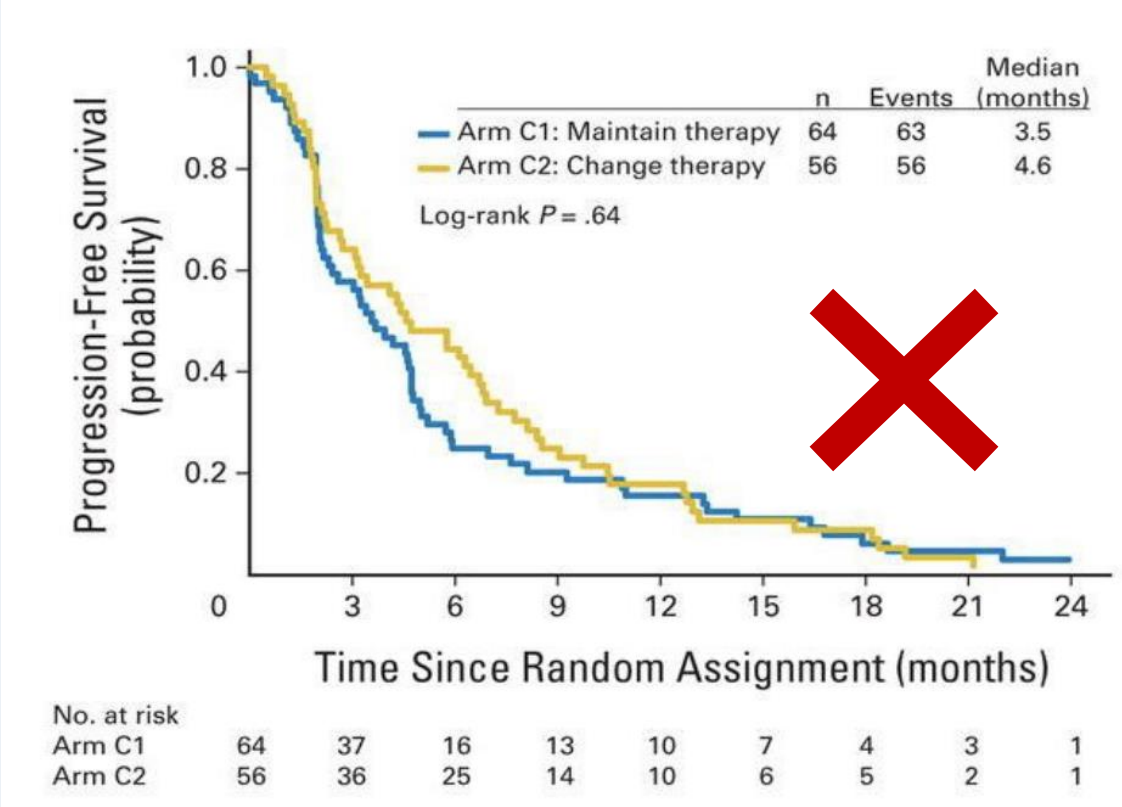
Trial	Population	MRD Assay	Intervention	Primary End Point
ASPRIA (NCT04434040)	TNBC residual disease, MRD+	Signatera Exome	Sacituzumab govitecan + atezolizumab	18-wk ctDNA clearance
KAN-HER2 (NCT05388149)	ERBB2+ residual disease, MRD+	RaDaR	Neratinib added to T-DM1	12-wk ctDNA clearance
PERSEVERE (NCT04849364)	TNBC residual disease	Foundation Medicine	Talazoparib, pembrolizumab, or inavolisib ± SoC	2-yr DFS
PREDICT-RD (TBCRC-071)	High-risk TNBC with RCB II/III after NAT	Signatera Genome	Datopotamab deruxtecan (Dato-DXd) for 8 cycles	MRD proportion; secondary RFS/OS

De-escalation / MRD-negative strategies

Trial	Population	MRD Assay	Intervention	Primary End Point
Safe-De (NCT05058183)	TNBC / ERBB2+, stage I, MRD–	Signatera Exome	Chemo omitted if MRD–; delayed treatment if MRD+	iDFS & DRFS (MRD– pts)

Can Molecular Relapse Become Treatable Relapse?

SWOG-0500: RCT Testing Therapy Change Based on CTC Status (Metastatic breast cancer)



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JOURNAL OF CLINICAL ONCOLOGY
ASCO SPECIAL ARTICLE

Breast Cancer Follow-Up and Management After Primary Treatment: American Society of Clinical Oncology Clinical Practice Guideline Update

James L. Khatcheressian, Patricia Hurley, Elissa Bantug, Laura J. Esserman, Eva Grunfeld, Francine Halberg, Alexander Hantel, N. Lynn Henry, Hyman B. Muss, Thomas J. Smith, Victor G. Vogel, Antonio C. Wolff, Mark R. Somerfield, and Nancy E. Davidson

- Use of CBCs, chemistry panels, bone scans, chest radiographs, liver ultrasounds, computed tomography scans, [^{18}F]fluorodeoxyglucose–positron emission tomography scanning, magnetic resonance imaging, or tumor markers (carcinoembryonic antigen, CA 15-3, and CA 27.29) is not recommended for routine breast cancer follow-up in an otherwise asymptomatic patient with no specific findings on clinical examination

Highly accurate diagnostics paired with highly effective therapies

Smerage JB, et al, JCO 2014; Parsons H, ESMO Breast 2026;

Scanxiety is real

And now testxiety…

Is it fair to test if we don't have the answers?

Logistical Challenge

$ Financial burden

Adds cost and out-of-pocket expenses; coverage varies by insurer and institution

↑ Testxiety

Positive results increase anxiety, especially when actionability is unclear

+ Cascade testing

A positive ctDNA may trigger additional imaging and invasive workup

Scientific Dilemma

Rx Premature therapy

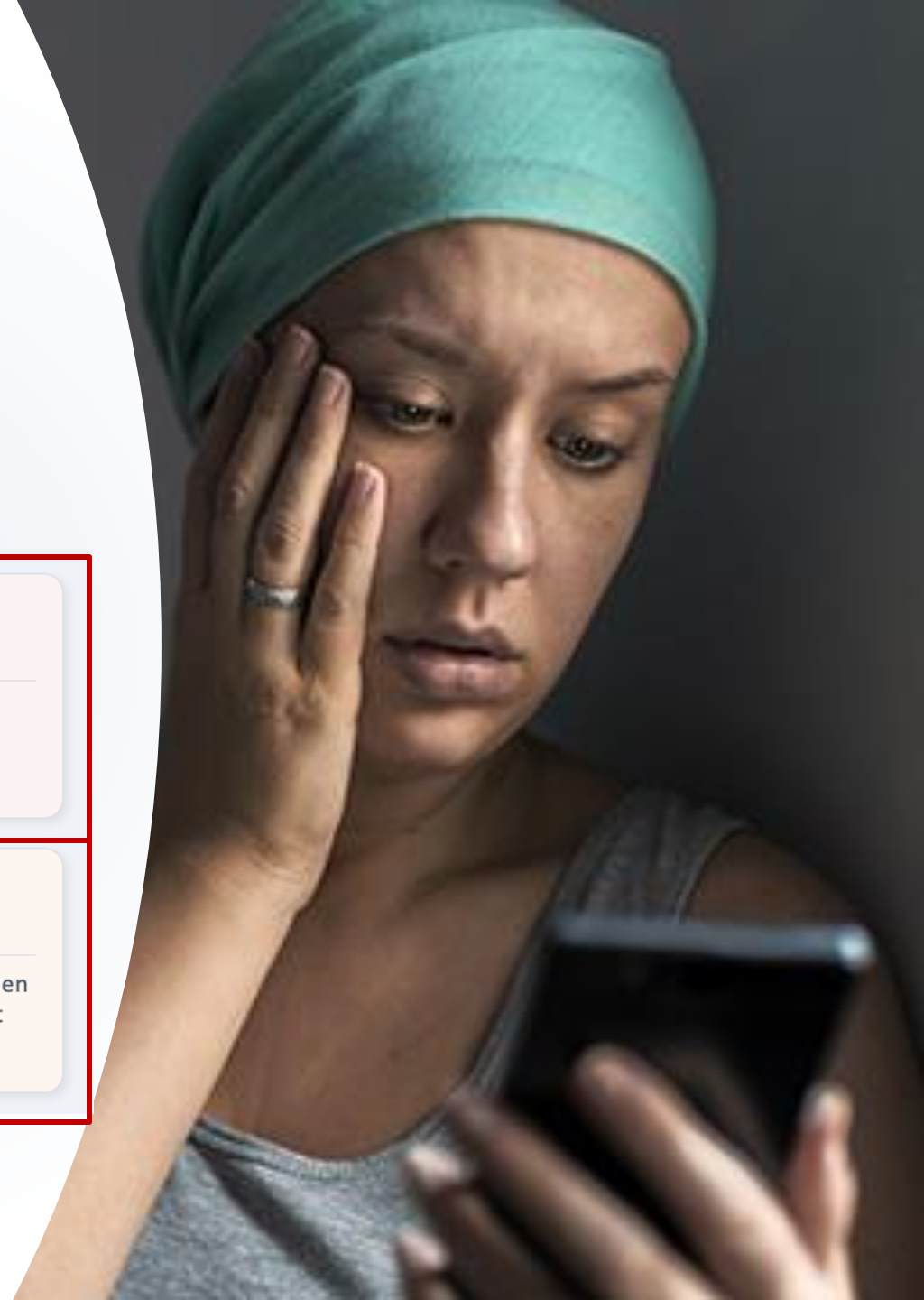
Asymptomatic patients may receive unnecessary treatment, affecting quality of life

⚠ Clonal selection

Early treatment may select resistant clones and limit future options

? Unproven OS benefit

Earlier intervention has not yet been shown to improve survival in most settings



How I Discuss ctDNA Testing in Clinic

Signatera, Pathlight, NeXT Personal reimbursed by Medicare for stage II-III breast cancer.

Honest and Balanced Discussion of Clinical Utility Evidence	• **Prognostic** • Earlier detection of oligometastatic disease • MRD guided treatment intensification not standard of care yet
Implications of a Positive Result	• Higher risk of recurrence, reflex imaging needed, closer surveillance • Emotional burden • **CLINICAL TRIALS !!!!!**
Implications of a Negative Result	• Does not implicate cure • Can still relapse (false negatives) • **Longitudinal monitoring (not just one test)**

ctDNA: The Promise is Real, the Proof is Pending

Caution Today

Forward-Looking Future

Q&A